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INTRODUCTION TO SERIES OF PAPERS ON STUDIES ON ACTH AND CORTISONE

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Received for publication August 1, 1950

INTRODUCTION

It was not until the studies of von Pirquet (1) on serum sickness were carried out in the early part of this century that interest in the hypersensitive state as a factor in certain human diseases became widespread. Since that time the term "allergy" has encompassed many diverse phenomena. The list of substances capable of inducing hypersensitivity is no longer confined to foreign proteins but contains a host of simple chemical substances, organic products of micro-organisms, and complex chemicals as well. Many are not true antigens but they are all "allergic excitants" and apparently the simpler materials can combine with body proteins to form the antigenic complex.

Manifestations of sensitivity in the human subject may take a variety of forms. One is the familiar flare-and-wheal reaction following the release of "H-substance" by a local antigen-antibody reaction. This type is seen in dramatic form in those patients who develop giant urticaria.

In the tuberculin type of hypersensitivity reaction the tissue response develops slowly and progressively, tending to persist for several days. In the anaphylactically sensitized subject the smooth muscles are incited to spasm on contact with antigen, a phenomenon which does not result from the tuberculin type hypersensitivity. It has been demonstrated that tissue cells may be damaged at the sites of injection and die, this necrosis being the result of vascular damage interfering with cellular nutrition in anaphylactic hypersensitivity, but due to an intrinsic cellular susceptibility in the tuberculin type of reaction. In the anaphylactic type of allergy the essential factor is the presence of a specific antibody which can react with the foreign antigens. Such antibodies can be demonstrated by precipitin test and by passive transfer. In the tuberculin type reaction there is no definite proof that there are any humoral antibodies and the cells themselves are the seat of the antigen-specific sensitization.

Although it is true that the clinical manifestations of allergy are very diverse the specificity which is characteristic makes it unlikely that there are many fundamentally different mechanisms by means of which the tissues react to various allergens. It is probably by the production of antibody that the stage is set for the allergic inflammatory reaction that results from the contact with the exciting antigen.

Both the anaphylactic and tuberculin types of hypersensitivity are of growing interest as far as their relationship to a variety of disease processes is concerned. The mechanism of the cellular damage in the delayed tuberculin reaction is not well understood. However, in the anaphylactic variety, which is so often accompanied by a mysterious eosinophilia of the blood and tissues, the effects may be produced by changes in the vascular endothelium, smooth muscle cells, or collagenous tissue. Endothelium becomes more permeable and may undergo necrosis; smooth muscle fibers undergo spasmodic contraction; and collagen may be the seat of degeneration and fragmentation. One of the concepts of particular clinical interest is that of the so-called "shock organ" which serves to categorize the various types of allergic reaction seen in human subjects. In asthma it is the glands of the bronchial mucous membrane which secrete heavily and whose smooth muscle becomes spasmodic. When the vascular endothelium is the site of the reaction one sees a variety of clinical resultants such as urticaria, angioneurotic edema, and purpura. In dermatitis and eczematous reactions it is the epidermal cells. What actually takes place in the tissues that sets up the allergic inflammatory reaction is not very well understood. Some investigators have felt that a direct injury to cells resulted from the union of antigen and antibody with the liberation of histamine, acetylcholine or other physiologically active substances, while other theories have postulated the inactivation of an enzyme inhibitor normally present with a resultant release of proteolytic enzyme activity, which in turn attacks the cells freeing these physiologically active substances.

In addition to well known examples, such as serum sickness, asthma, and drug hypersensitivity where the antigenic substance is known and a specific relationship can be established the belief has been growing that the anaphylactic type of hypersensitivity may play a basic role in the pathogenesis of certain disease states. As early as 1913 Wein-

traud (2) made the then rather unique suggestion that the lesions of rheumatic fever resulted from anaphylactic reaction to bacterial products liberated in the tissues of the patient sensitized by infection. A variety of authors attempted to produce the lesions of rheumatic fever by injecting bacteria into the tissues of sensitized animals but the results were not altogether convincing. However, in a series of papers published from 1913 to 1915 Longcope (3) demonstrated that when repeated injections of protein were made into animals areas of degeneration with extensive inflammatory reaction were produced in the myocardium, liver and kidneys. These consisted in focal areas of degeneration, infiltrated with round cells, which in the heart were scattered throughout the myocardium, in the liver usually situated about the portal spaces, and in the kidney in the cortex. These changes occurred after a period of ten to twenty-one days, sufficient time for the animal to form antibodies for the foreign protein.

In 1925 Gruber (4) suggested that periarteritis nodosa might be due to hypersensitivity and later Vaubel (5) found lesions which he compared to those of periarteritis nodosa in animals who received injections of a foreign protein. In 1937 Clark and Kaplan (6) noted vascular lesions in two patients who had serum sickness just before death but they were hesitant to attribute this injury to the hypersensitivity. Widespread periarteritis nodosa was found by Eason and Carpenter (7) in a patient who died nineteen days after the onset of serum disease. This relationship, however, was never clear until the widespread use of sulfonamides greatly increased the opportunity for pathological study of the effects of the serum sickness type of anaphylaxis on human tissues. Rich and Gregory (8) obtained conclusive evidence that the periarteritis nodosa seen in a variety of drug and foreign protein reactions is a manifestation of the anaphylactic hypersensitivity. The relationship was amply confirmed by these workers when they were able to produce widespread lesions typical of periarteritis nodosa in rabbits by inducing a sensitivity reaction to horse serum. The human pathological studies were expanded and this classical type of periarteritis nodosa has been seen in patients dying as a result of hypersensitivity to iodine, thiourea, dilantin and other substances (9).

In the hearts of some animals who had developed serum sickness Rich and Gregory encountered lesions which were very similar in their

anatomic characteristics to those seen in patients dying with rheumatic carditis. Rich reemphasized the fact that rheumatic fever and disseminated lupus erythematosus displayed a rather impressive group of phenomena known to occur as a part of the anaphylactic reaction in serum sickness, including sterile and migratory pulmonary consolidations of a characteristic type. Focal collagen degeneration of the anaphylactic type is well known in rheumatoid arthritis and is the basic lesion of the subcutaneous nodules seen in this disease. It is well known that a given antigen in different individuals may produce such widely divergent reactions as urticaria, asthma, purpura and arthritis. The actual mechanisms that determine these differences are obscure but such factors as heredity may play a part. Such differences may determine the type of clinical picture that the patient will develop in the group of diseases in which the prominent lesions are collagen and vascular tissue injury. These stimulating observations of Rich and others emphasized the need for a better understanding of the basic mechanisms of hypersensitivity and the importance of careful investigation of the possible role of sensitization in the pathogenesis of a wide variety of human diseases.

When the work of Hench and his coworkers (10) was announced in April, 1949 the relationships described above indicated that adrenocorticotropic hormone (ACTH) and cortisone might be an important tool in the study of various hypersensitivity reactions. A patient critically ill with exfoliative dermatitis due to iodine hypersensitivity was treated with ACTH with a rather dramatic result. This led us to embark on a program to test the clinical effects of ACTH and cortisone in hypersensitivity reactions due to a wide variety of antigens affecting different "shock organs" and in those so-called collagen vascular diseases having a variety of phenomena in common with serum sickness of the anaphylactic type. Studies on the basic mechanisms involved are in progress and the following series of papers will describe the clinical observations in detail. The material has been divided into the following sections:

1. The Effect on Drug Hypersensitivity Reactions.
2. The Treatment of Chronic Intractable Asthma.
3. The Effect on The Mucous Membranes and Lymphoid Tissue in The Nasopharynx.

4. The Treatment of Disseminated Lupus Erythematosus and Periarteritis Nodosa.
5. The Effect on Certain Diseases of the Eye in which Hypersensitivity Plays a Role.
6. Experimental Observations on Certain Hypersensitivity Phenomena in the Eye.

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THE EFFECT OF ADRENOCORTICOTROPIC HORMONE (ACTH) AND CORTISONE ON DRUG HYPERSENSITIVITY REACTIONS

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INTRODUCTION

Hypersensitivity to chemical substances used in medicine is a common phenomenon, and its manifestations vary in significance from minor skin eruptions to severe and fatal reactions. In addition to the conditions generally recognized to be due to sensitization, such as urticaria, angioneurotic edema, other types of cutaneous eruption, asthma, arthritis, lymphadenopathy, fever, and leucocytosis, other severe abnormalities such as agranulocytosis, thrombocytopenia with purpura, and hepatitis may result. Both the intracutaneous tests for hypersensitivity and the classical methods to demonstrate circulating antibodies were developed from studies of protein antigens and are not in most instances applicable to allergens of low molecular weight such as crystalloid drugs. However, in most instances readministration of the drug will induce the sensitivity reaction at an accelerated rate.

In the present communication the effect of ACTH and cortisone on the signs and symptoms of hypersensitivity to certain drugs in human subjects will be described and in certain instances the effect of readministration of the specific substance during the exhibition of these hormones. Clinical observations will be reported on hypersensitivity reactions to iodine, sulfonamides, penicillin, acetylsalicylic acid, hydroxy-phenyl-cinchoninic acid, and atropine (Table 1). In addition studies on a case of paroxysmal (cold) hemoglobinuria in which urticaria appeared after chilling will be described. Certain of these results have been summarized in preliminary communications (1, 2, 3).

RESULTS

Hypersensitivity to iodine: It is generally recognized that certain patients under treatment with iodine develop hypersensitivity to this element. The manifestations include cutaneous eruptions and, as Barker and Wood (4) have pointed out, others of the "serum sickness" type of hypersensitivity such as fever, arthralgia, lymphadenopathy and eosinophilia. Rich (5) has reported a case in which iodine sensitivity caused the destructive vascular lesions of periarteritis nodosa. The following case report describes the effect of ACTH on the clinical course of an unusually severe hypersensitivity reaction to iodine with high fever, and extensive exfoliative dermatitis.

J. C. (JHH 503368).

A thirty-four year old colored laborer entered the hospital on June 5, 1949 complaining of fever, chills, and pain in the right lower chest of five days duration. For several years he had had frequent severe "colds" with fever, sweats, and cough productive of blood streaked sputum.

On examination there were signs of patchy consolidation in the right lower lobe, a pleural friction rub was present as well as evidence of a small accumulation of fluid in the pleural cavity. There was a moderate degree of anemia with hemoglobin 12 grams, red blood cell count 3.7 million and hematocrit 39 per cent. The white blood cell count was 21,000 with juveniles 14%, and adult polymorphonuclear cells 75%. X-ray examination confirmed the physical findings. Examination of the sputum revealed a type 2 pneumococcus. It was presumed that the patient had an acute pneumonitis superimposed on a chronic bronchiectasis.

The patient was placed on penicillin therapy; the temperature fell to normal within 48 hours. On June 11 syrup of hydriodic acid was prescribed 12 cc. daily and on June 19 penicillin was discontinued.

July 4, the patient developed an itching, erythematous, maculo-papular eruption which gradually increased in severity but was symptomatically relieved by the administration of pyribenzamine. July 7 the hydriodic acid was discontinued; the following day the patient's temperature rose to 105°F. The eruption became confluent, extensive ulcerative lesions developed on the mucous membranes of the mouth with swelling of the submaxillary glands, and marked angioneurotic edema involving the face, lips, tongue, eyelids, hands and arms. The high continuous fever persisted. On July 11 the patient became completely disoriented. The lids of both eyes were very swollen with a profuse purulent discharge and marked ectropion of the lower lids (Fig. 1, lt.). There was progressive ulceration of the tongue and buccal mucous membranes and extensive balanitis. The patient had a severe cough, productive of large quantities of muco-purulent sputum which soon became blood-tinged. Aureomycin had no effect on the course of the pyrexia.

TABLE 1

Summary of the Cases Described in this Report

CASE	AGE	SEX	RACE	CAUSE	CLINICAL MANIFESTATIONS	TOTAL DOSE ACTH CORTISONE	DURATION TREATMENT	RESPONSE	RELAPSE DAYS AFTER TREATMENT
						mgm	*days*		
J. C. JHH 503368	34	M	C	Iodine	Fever, exfoliative dermatitis, angioneurotic edema, stomatitis, balanitis, bronchitis, toxic psychosis	900	7	Prompt, complete. Retreated after relapse successfully with very mild recurrence	6
J. A. JHH 515854	26	F	W	Penicillin	Urticaria, angioneurotic edema, arthritis	150	3	Prompt and complete	None
E. S. S. H. 48580	26	M	W	Penicillin	Fever, lymph node enlargement, urticaria, angioneurotic edema, arthritis	500	7	Prompt and complete	5
B. D. JHH 521686	72	M	W	Penicillin	Urticaria, angioneurotic edema	785	9	Prompt and complete	8
F. R. JHH 426648	44	M	W	Penicillin	Urticaria, angioneurotic edema, erythema multiforme	340	3	Prompt and complete	None
P. H. JHH 336771	52	M	W	Question due to Penicillin	Chronic urticaria	895	9	Delayed, complete. Successful treatment again after relapse	14
C. N.	44	M	W	Penicillin	Fever, urticaria	1000	4	Delayed, residual der-	10

				Penicillin				after relapse	
C. N. JHH 489584	44	M	W	Penicillin	Fever, urticaria, angioneurotic edema	1000 (Cortisone)	4	Delayed, residual dermatographia	10
J. W JHH 532752	40	F	W	Atropine. Tuberculous uveitis	Dermatitis, lids and face	1420	14	Moderately rapid and complete. Uveitis subsided. Patch test almost completely blocked	None
S. L. JHH 523497	62	F	W	Atropine. Sympathetic ophthalmia	Dermatitis of lids, conjunctivitis			Atropine reaction blocked at doses above 20 mgm. per day	
J. R. JHH 517189	55	M	C	Sulfapyridine	Fever, dermatitis, nephritis, agranulocytosis	300	6	Total white count and percentage granulocytes rose	Died
J. M. HLH A-74909	7	M	W	Sulfadiazine	Fever, exfoliative dermatitis, leucopenia	780	6	WBC returned to normal. Dermatitis healed faster. New lesions ceased to form	Incomplete response when drug stopped
K. L. JHH 464514	36	M	W	Hydroxy phenyl cinchoninic acid. Cutaneous lupus erythematosus	Fever, coryza, skin eruption	2900	18	Challenged repeatedly with drug. See text	
J. F. JHH 528483	28	M	W	Acetyl-salicylic acid. Chronic asthma	Severe asthma after ingestion of aspirin			Challenged repeatedly with aspirin. See text	
M. E. JHH 414118	33	F	C	Paroxysmal (cold) hemoglobinuria	Urticaria after chilling	450	5	Appearance of urticaria blocked. Hemolysis unaffected	

By July 16 there was extensive exfoliation with denuded, raw areas over the elbows and back.

ACTH (Searle) 100 mgm. (25 mgm. every six hours) was begun on this day and continued for nine days. By July 18 the temperature had fallen to 100°F (rectal) and the skin showed marked improvement with less edema; a thin epithelium covered all areas except the right elbow and both antecubital spaces. The following day the patient was more alert and took fluids well by mouth. July 20 he was able to feed himself, there was less photophobia and he could open his eyes well.

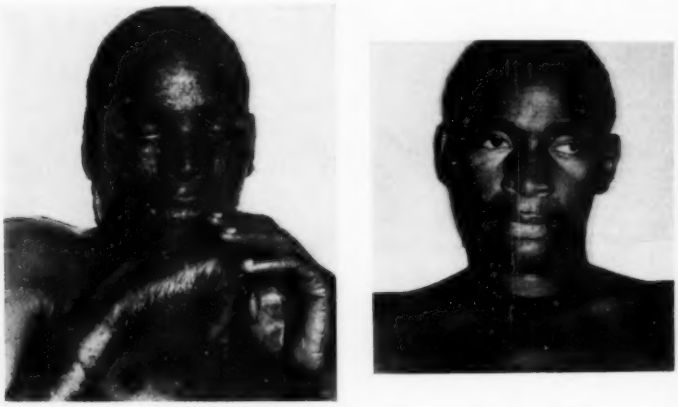

FIG. 1. J. C. (JHH 503368) HYPERSENSITIVITY TO IODINE. TREATMENT WITH ACTH.
Left: Before treatment (see text).
Right: Fifth day of treatment (see text).

All areas of skin were now epithelialized and the edema was almost completely gone (Fig. 1, rt.). By July 24 when ACTH was discontinued the ectropion had entirely disappeared, all areas of the skin were healing well, with minimal residual exfoliation.

On July 30 the temperature reached 103°F, his mental status was again abnormal and the skin showed a recurrence of the exfoliation. ACTH therapy was reinstituted in daily doses ranging from 100 to 200 mgm. There was a prompt fall in temperature to normal, the patient again became alert, and dermal exfoliation ceased. The last dose of ACTH was given on August 5.

August 16 it was noted that he had gained weight, had an excellent appetite. There was slight return of the cutaneous exfoliation particularly noticeable after bathing. This continued for several weeks, gradually subsiding.

Summary: This patient was critically ill with high fever, extensive angioneurotic edema, ulceration of buccal mucous membranes, exfoliative dermatitis and disorientation. All who saw him were greatly impressed by the rapidity with which his condition improved when ACTH therapy was instituted. The moderately severe relapse which followed the first course of ACTH and the prompt recovery when the hormone was readministered seemed to establish the effect as more than coincidental.

Reactions to Penicillin of the Serum Sickness Type: Delayed anaphylactic reactions to penicillin of the serum sickness type are not uncommon. In severe cases symptoms may persist for several weeks after discontinuance of the drug. Various studies have shown that neither the skin test nor passive transfer reaction is a reliable index of penicillin sensitivity (6). Skin reactions to penicillin may occur in non-sensitive individuals and there may be complete absence of reaction to intradermal injection of the drug during or shortly after an extensive urticarial reaction following parenteral administration.

In five patients treated with ACTH during the height of the sensitivity manifestations very dramatic relief was evident in a few hours. In one patient to whom large doses of cortisone were given there was a definite beneficial response which was delayed and not as complete as with ACTH therapy. Recurrence of urticaria five to fourteen days after stopping treatment in four of the six cases indicated that the improvement was most likely not coincidental and that the sensitivity itself had not been eliminated.

J. A. (JHH 515854).

A 26 year old medical secretary was admitted on September 29, 1949 complaining of urticaria and angioneurotic edema of 18 hours duration. There was no family or personal history of any allergic manifestations. Nine months previously she had taken four tablets of penicillin orally.

For one week before admission she had had left frontal and ethmoid sinusitis, confirmed by radiological examination. Her symptoms persisted and at 3 p.m. on September 28 she was given 300,000 units of crysticillin intramuscularly. At 9 p. m. there appeared a generalized urticaria most extensive over the arms, legs, and buttocks. A few hours later she complained of pain in the mid-thoracic region posteriorly, radiating to the xyphoid process. She was nauseated and vomited. The following morning there was pain and stiffness of the fingers, wrists, ankles, elbows, and right knee. The arthritis became progressively more severe and severe angio-

neurotic edema of the fingers and hands developed. A ring was cut off to prevent gangrene.

On examination the temperature was 99.6°F (rectal). There was severe, tense edema of both hands, and wrists. Both elbows and ankles were swollen and tender. The dorsum of the right foot was tensely edematous. There were numerous erythematous cutaneous lesions many of which were purpuric. There was extensive cutaneous hemorrhage along the skin folds of the hands. Many erythematous and hemorrhagic macules were seen on the soft palate. There was no lymph node enlargement. The leucocyte count and differential were normal. There were 22 eosinophils per cu. mm.

Beginning at 6 p.m. on September 29, 12.5 mgm. of ACTH (Armour) was administered every 6 hours. The following morning the patient was able to flex all of her joints with ease, the edema, which had been increasing at a rapid rate, was less evident, and the tenseness of the skin had subsided. The fingers, which had been cold and numb, were now warm with normal sensation. Tenderness over the joints had subsided. By the morning of October 1 the edema had entirely subsided and the only residuum was the discoloration of the purpuric lesions, which had begun to fade a few hours after treatment was started. The dose of ACTH was rapidly tapered and then discontinued completely. There has been no recurrence of symptoms.

This patient received a total of 150 mgm. of ACTH over three days. During this period the eosinophil counts were zero.

Summary: This patient had an accelerated serum sickness-like reaction to penicillin with arthritis, urticaria, angioneurotic edema, and hemorrhagic cutaneous lesions. Under ACTH (50 mgm. a day) the lesions disappeared rapidly and completely with no recurrence.

E. S. (Sinai Hospital 48580).

This 26 year old house officer was admitted to the hospital on September 19, 1949 complaining of pruritus, urticaria and arthralgia of eleven days duration.

In July, 1947 he received 1.0 million units of aqueous penicillin intramuscularly over a three day period as treatment for a periorbital cellulitis. August 31, 1949 a tooth was extracted and one-half tablet of penicillin placed in the socket. The same day he received 300,000 units of crystalline penicillin G and a similar amount of depo-penicillin intramuscularly. The following day he was given a second dose of the depo-penicillin.

September 8 he developed pruritus over the buttocks followed by urticaria and induration of the skin. Pain and swelling developed in both elbows, the right wrist and both feet. From this time on he had migratory joint pains and swelling as well as numerous crops of hives. There was some angioneurotic edema involving the eyelids, face, and soft palate. Adrenalin, and anti-histaminics gave no relief and he was finally admitted to the hospital on September 19.

FIG. 2. E. S. (S.H. 48580) Hypersensitivity to Penicillin; showing the extensive giant urticaria which subsided within a few hours after beginning ACTH therapy (see text).

Physical examination on admission revealed temperature 100°F (rectal), pulse 100, respirations 18 and blood pressure 115/80. The patient was very uncomfortable with marked pruritis but was not seriously ill. There was swelling and redness of both eyelids and numerous urticarial lesions were present over the frontal and temporal areas. There were myriads of giant urticarial lesions, many of the annular type, scattered over the body and all four extremities (Fig. 2). There was slight generalized enlargement of the lymph nodes. There was tenderness on movement of the left shoulder, the left elbow, the right wrist and the right middle finger and thumb with some swelling of the latter two joints. The remainder of the examination showed no significant abnormalities. The white cell count was 12,000 with 4% eosinophils.

Therapy with adrenalin and anti-histaminic drugs was continued, but there was a progressive increase in the severity of his sensitivity manifestations.

September 21 the patient's temperature reached 101.6, he had generalized urticaria and some edema of the posterior pharynx. The lymph nodes became larger. On September 23 pitting edema was noted over the forearms and hands. The left thumb was then swollen, red, and tender.

At noon all symptomatic therapy was stopped and ACTH (Armour) was begun (25 mgm. every six hours). Four hours later the urticarial wheals showed definite blanching, and the temperature had dropped to normal. After 12 hours the wheals had lost their erythematous appearance and were flattened. The joint pains had disappeared. The following morning no hives were visible, the pruritus had ceased to be troublesome and the edema was gone. No new lesions formed after ACTH therapy was started. The enlargement of the lymph nodes was not detectable by the second day of treatment.

On September 26 after intradermal testing with one unit and fifteen minutes later with ten the patient was given intramuscular injections of 100 and then 1000 units of aqueous penicillin G two hours apart. There was no immediate reaction to any of these test doses.

The ACTH dosage was gradually tapered and the drug stopped on September 30. A total of 500 mgm. had been administered.

On October 4 the patient developed transitory erythema and itching of both feet. October 7 there was urticaria and edema of the right hand, pain in the left wrist and that evening, generalized urticaria and some swelling of the lips. Temperature was 101. The cutaneous manifestations were adequately controlled with adrenalin but mild outbreaks of urticaria continued until November 15, 1949.

Summary: This patient had a very severe and persistent serum sickness-like reaction to penicillin which cleared dramatically on ACTH therapy. There was no immediate reaction to 1000 units of penicillin intramuscularly during ACTH treatment but the sensitivity manifestations reappeared eight days after this test dose and five days after ACTH had been discontinued.

B. D. (JHH 521686).

This 72 year old white man entered the hospital on November 23, 1949 complaining of severe urticaria.

One week previously he had developed a sore throat. His local physician gave him a daily intramuscular injection of penicillin on each of three days. He had received this drug previously but did not remember the exact time or the amount.

Two days after the last injection he developed moderately severe urticaria over the buttocks and thighs with marked redness and itching of the palms of his hands. The urticarial lesions spread, the sore throat persisted, and there developed severe lancinating pains radiating from the submandibular area to the region of the right ear. Adrenalin and pyribenzamine afforded no satisfactory symptomatic relief.

On admission the temperature was normal. The patient was very uncomfortable because of itching. There was slight periorbital edema and some edema over the buttocks. There were large giant hives over the buttocks, upper thighs and abdomen. There were smaller cutaneous lesions over the forehead and tibiae as well as reddening and induration of the skin over the right thenar eminence. The pharynx was red and there was a small ulcerated area in the right tonsillar fossa which felt indurated on palpation. A lymph node was palpable below the right mandible; pressure over which precipitated the pain referred to the right ear.

The cutaneous lesions persisted with intense pruritus. November 23 at 10 p.m. ACTH (Armour) therapy was begun. At 4 a.m. it was noted that the intensity of the erythema had decreased greatly and the hives were flattening. By 9 a.m. the itching had gone, and the wheals had disappeared leaving a faintly pigmented area with a bronze coloring. The lymph node was no longer palpable, pressure in the submandibular area did not evoke pain, and there were no further spontaneous attacks. By the second day the residual discoloration had faded and the periorbital edema had disappeared.

November 26 while still receiving ACTH the patient was given 5,000 units of aqueous penicillin intramuscularly and on the following day 50,000 units. November 28 there was slight itching and a small area of erythema around the site of injection. This had disappeared by the next morning. The ACTH dosage was rapidly tapered and the patient was discharged on December 3. He had received a total of 785 mgm. (Armour) over a nine day period, the maximum dose being 100 mgm. per day. The eosinophil count was 44 per cu. mm. before treatment and remained at zero during the period of therapy.

Eight days after discharge a generalized urticaria suddenly developed. The lesions were much smaller and less severe symptomatically than the original ones. 100 mgm. of neohetramine were given every four hours and within twenty-four hours the lesions had faded. The dose of neohetramine was gradually reduced over a four day period and then stopped. There has been no recurrence.

Summary: This patient had severe urticaria appearing five days after starting penicillin therapy. The urticaria disappeared rapidly and completely when ACTH therapy was instituted. Challenge with

50,000 units of penicillin produced only a slight erythematous reaction at the injection site. Fifteen days after this challenging dose and eight days after discontinuance of ACTH there was a mild, fleeting recurrence of the urticaria.

F. R. (JHH 426648).

This 44 year old physician entered the hospital March 26, 1950, complaining of persistent urticaria and subcutaneous nodules with erythema of the overlying skin of 10 days duration.

The family history was non-contributory but the patient had had hay fever for many years. He had received intramuscular injections of penicillin in 1945 and had used penicillin lozenges during an upper respiratory infection in December, 1949. March 6, 1950 a cholecystectomy and appendectomy were performed and for the following five days he received aqueous penicillin G 200,000 units and 0.5 grams of dihydrostreptomycin every eight hours without any immediate ill-effects.

On March 16 he noted several "lumps" over his scalp. The following day there was extensive swelling over the forehead and considerable periorbital edema. The feet and ankles became swollen and tender, there was thickening in the region of the Achilles tendon on the right, and scattered tender subcutaneous nodules appeared on the elbows, knees, and hands. On March 19 the right wrist and dorsum of the hands became swollen, tender and stiff. Scattered hemorrhagic lesions appeared in the skin and finally a cluster of large vesicles on the ventral surface of the right forearm. During a period of nine days before admission large doses of pyribenzamine and adrenalin-in-oil were administered without much symptomatic relief and new lesions of an urticarial nature continued to appear. Pruritus was persistent; the patient was fatigued and unable to carry out his work as an ophthalmologist.

Physical examination on admission revealed temperature 99°F (rectal), pulse 92, respirations 16 and blood pressure 130/80. Both cheeks and periorbital regions were puffy. The right hand and fingers were swollen with pitting over the dorsal surface, tenderness to pressure, and increased warmth. There was slight swelling and erythema of the left hand. A cluster of vesicles each with an erythematous base surrounded the right wrist (Fig. 3, rt.). The entire right forearm and a portion of the upper arm were swollen to twice normal size (Fig. 3, lt.). There were numerous firm, tender erythematous nodules over the skin of the right forearm and hand, the right foot, and over the lumbosacral region. The general physical examination showed no other significant abnormalities. The total white cell count was 10,200 with 187 eosinophils per cu. mm.

All medication was discontinued and during the first 24 hours in the hospital the edema increased and new cutaneous lesions appeared. March 27 at 8 a.m. the eosinophil count was 330. Treatment with ACTH (Armour) 25 mgm. every six hours began at 6 p.m. on that day. At nine a.m. March 28 the eosinophil count

was 253. On that day the erythema was less and no new lesions appeared. The following day the ACTH dosage was increased to 35 mgm. every 6 hours. Following this the eosinophil count fell to 66. Clinical improvement was very rapid with complete disappearance of the edema and the cutaneous lesions within 36 hours. The total dose of ACTH over the three day period was 340 mgm. No new lesions appeared and manifestations of hypersensitivity have not recurred (May 15). There was a gain in weight of one and a half pounds during ACTH administration

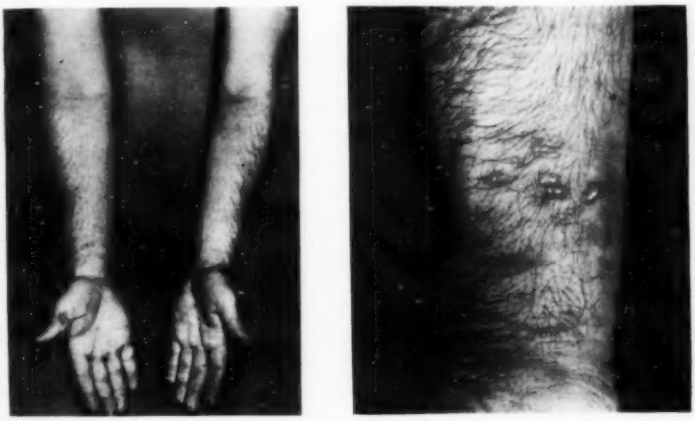

FIG. 3. F. R. (JHH 426648) Hypersensitivity to penicillin before treatment. Photograph on left shows the edema of the right arm. On the right is a closer view of the cutaneous lesions with vesiculation. These changes subsided rapidly under treatment with ACTH (see text).

despite the disappearance of the extensive angioneurotic edema which involved almost the entire right arm.

Summary: This 44 year old physician developed a severe reaction to penicillin five days after the last dose, characterized by extensive angioneurotic edema, urticaria and lesions resembling erythema nodosum and erythema multiforme. After ten days of treatment with pyribenzamine and adrenalin-in-oil, during which there was no relief and new lesions continued to appear, he received 340 mgm. of ACTH over a period of three days. There was a complete remission of the lesions within 36 hours and there has been no recurrence.

P. H. (JHH 336771).

This 52 year old white male was admitted to the hospital on April 26, 1950 with the complaint of "hives" of approximately five months duration.

The patient's father had asthma but the patient had had no known allergic manifestations.

Six months prior to entry he developed a penile lesion for which he was treated with ten daily injections of "penicillin in oil." Just before the eleventh injection generalized urticaria appeared and since that time he has never been more than two to three days without these lesions. The only previous exposure to penicillin was several years previously when he took penicillin troches. During the several months prior to admission various types of therapy were administered without relief including: antihistaminics, adrenalin, calcium gluconate, and injections of histamine subcutaneously.

Physical examination at the time of admission showed nothing remarkable other than a slight generalized lymph node enlargement and numerous small urticarial lesions. There was rather marked dermatographia.

During the next three weeks in the hospital he continued to have numerous crops of urticarial lesions in various areas of the skin. Pruritus was constant and wheals always appeared along the scratch marks. During this period he received hydroxyphenyl-cinchoninic acid, pyribenzamine and intravenous injections of histamine with no benefit.

On May 18 ACTH (Armour) therapy was started 25 mgm. every six hours. The following day hives were still present but the circulating eosinophils had only decreased from 242 per cu. mm. to 165 per cu. mm. The ACTH dosage was then raised to 30 mgm. every six hours. During the next four days severe pruritus continued and numerous crops of hives appeared although on May 22 there were no circulating eosinophils and the fasting blood sugar had risen from 92 to 140 mgm. per cent.

On May 23 the patient was free of urticaria for the first time although some pruritus remained and the dermatographia was still evident. May 24 the dose was reduced to 20 mgm. every six hours, and there was no urticaria, pruritus, or any abnormal degree of dermatographia. May 25 a total of 60 mgm. of ACTH was administered and the last treatment, 40 mgm., was given on May 26.

June 1, the day before discharge, he complained of slight pruritus but scratching produced no wheal formation.

He was placed on small doses of pyribenzamine. June 10 he had a recurrence of urticaria which has persisted up until the last visit on June 17.

Summary: This 52 year old white male had chronic urticaria of six months duration which had begun after the administration of penicillin and had been resistant to a variety of therapeutic regimes.

A total of 895 mgm. of ACTH was given over a period of nine days. On the fifth day of treatment, 24 hours after circulating eosinophils

disappeared from the blood, the skin became normal. The urticaria recurred fourteen days after ACTH was discontinued.

C. N. (JHH 480584).

This 44 year old white male was admitted on January 4, 1950 complaining of severe urticaria of three days duration. There was a history of ragweed hay fever and attacks of sinusitis over many years. Early in December, 1949, he had a recurrence of sinusitis and on December 15 was placed on eight tablets of aluminum penicillin (50,000 units each) orally a day. His symptoms continued and on December 27, 28, and 29 he was given 300,000 units of crysticillin intramuscularly. Pyribenzamine was given without relief of the nasal obstruction. December 28 to 30 the patient took another 14 tablets of penicillin orally.

January 2 he developed pruritus and the following day had slight edema of the hands, ears, and feet. Severe generalized urticaria appeared, and no symptomatic relief was obtained with adrenalin and large doses of pyribenzamine.

The temperature on admission was 102.4°F (rectal). The patient was in great discomfort with generalized pruritus. The skin of the trunk and extremities was covered with sharply demarcated urticarial wheals. The fingers and hands were edematous. The remainder of the physical examination showed no significant abnormalities. The total white cell count was 8,500 and there were only 11 eosinophils per cu. mm.

At 11 a.m. on January 4 the patient received 200 mgm. of cortisone acetate and then 50 mgm. every six hours. During the first two days there was no improvement. The temperature remained elevated and discomfort increased. The morning of January 7 temperature became normal and the urticarial wheals disappeared rapidly. Pruritus continued, there was some induration of the skin, and rather marked dermatographia persisted. On January 10 a few "welts" appeared on the back despite pyribenzamine therapy. Itching continued and on January 23 the patient had a few hives and his eyelids were slightly swollen. February 2 there was a recurrence of mild urticaria which was evanescent. There have been no symptoms since that time.

Summary: This patient had fever, severe urticaria and angioneurotic edema after taking penicillin both orally and intramuscularly over a period of several weeks. There was a sudden improvement on the third day of cortisone therapy with drop in temperature and subsidence of urticaria. However, at that time when the patient had gained eight pounds in weight and had developed acneiform lesions, there was still persistent pruritus and marked dermatographia.

Hypersensitivity to atropine: Irritation of the conjunctiva, lids and adjacent cutaneous surfaces following the instillation of various alkaloids into the eye has long been a recognized clinical entity (7, 8).

Atropine can combine with the protein of the tears to form stable salts to which patients with the drug sensitivity show a specific cutaneous reaction. The same type of reaction will appear in 24 to 48 hours after a cutaneous patch test with an ointment containing the alkaloid.

Clinically, the drug reaction varies from redness and edema of the conjunctiva, to a dry eczematous, cutaneous eruption which may cover the greater portion of the face on the involved side. There is an associated muco-purulent discharge from the conjunctival sac with the formation of heavy crusts over the involved surface of the skin.

The following cases illustrate the dramatic effect of ACTH on this type of reaction:

J. W. (JHH 532752).

This 40 year old white female entered the hospital on March 27, 1950 with uveitis in the left eye and a severe reaction to atropine involving the lids and the surrounding skin of the face. The iritis began in July, 1949, subsided after several weeks under local treatment, and recurred in October remaining active with periods of increased ocular tension. Posterior synechiae formed which could be released at first by the use of atropine locally. A cutaneous hypersensitivity to the atropine developed early in November. Scopolamine was substituted but hypersensitivity to this drug soon appeared also, and thereafter atropine was used only on occasions when the condition of the eye made it imperative. Pyribenzamine had no effect in controlling the cutaneous reaction to atropine which was extensive and severe. The uveitis grew rapidly worse and the cutaneous reaction to atropine became so intense that the patient was sent to Baltimore for a trial on ACTH.

At the time of admission there was a violent dermatitis due to atropine which involved the entire left side of the face and extended to the right side (Fig. 4, a) The lids were swollen and indurated and, because of pain, could not be opened sufficiently to allow a completely satisfactory examination of the eye. It was apparent that there was a violent pericorneal congestion, marked edema of the corneal epthelium, an infiltrate in the cornea, and posterior synechiae. The skin of the face was very red, extensively denuded, erythematous, edematous and covered with fresh and crusted exudations. The vision was limited to light perception. The right eye was normal.

General examination was normal. There was a violent reaction to the intracutaneous injection of 0.001 mgm. of tuberculin with an area of erythema and induration several centimeters in diameter. In the center of this reaction necrosis with sloughing developed. A patch test with atropine was done which produced a severe reaction identical with the facial lesions.

ACTH (Armour) therapy was begun on March 27. The patient received 25 mgm. every six hours for 3 days; 40 mgm. every six hours for 3 days; 30 mgm. every six hours for 3 days; 20 mgm. every six hours for 2 days; and 10 mgm. every

six hours for 3 days. The total dose was 1420 mgm. averaging 101.4 mgm. per day over the treatment period. A satisfactory response could undoubtedly have been obtained with smaller doses but this level was instituted to see if the skin reactions could be blocked.

Under treatment there was rapid healing of the skin lesions. The erythema and edema subsided and the raw areas epithelialized (Fig. 4, b). In view of the promptness with which these changes occurred and the failure of the lesions to

FIG. 4. J. W. (JHH 532752) HYPERSENSITIVITY TO ATROPINE, TREATMENT WITH ACTH.

Left: Before treatment. Note the swelling of the lid and the exudative dermatitis of the surrounding skin.

Right: Photograph taken in the immediate post-treatment period.

regress prior to therapy there seemed no doubt that the ACTH was responsible. With 48 hours the pericorneal congestion had faded, the corneal edema subsided rapidly, and the intraocular tension became stabilized. Slit lamp examination now showed some pigmented keratic deposits, one large fuzzy corneal infiltrate, some organized exudate on the anterior capsule of the lens, and a faintly positive aqueous flare. On the upper sclera near the equator a patch of subsiding deep scleritis could now be seen. The improvement was steady and by the time of discharge of April 12, the dermatitis had entirely cleared and the eye was completely free of inflammation. Vision had risen to 20/100.

On April 4 the patient was challenged with the same dose of tuberculin and the atropine patch test was repeated. She was completely negative to 0.001 mgm. of tuberculin and developed only a mild erythema 10 by 10 mm. to 0.01 mgm. Instead of the violent reaction to the patch test with atropine there was now only a faint erythema.

Summary: This patient who had tuberculous uveitis developed a severe reaction to locally applied atropine which involved the lids and the surrounding skin of the face. The cutaneous patch test to atropine was strongly positive. During ACTH administration there was rapid healing of the skin lesions and the patch test produced only a moderate erythema.

S. L. (JHH 523497).

This patient was a 62 year old white female who developed atropine hypersensitivity during local treatment for sympathetic ophthalmia. This was manifested by a dry, brawny thickening of the skin of the lids, conjunctival hyperemia and dry crusts along the cilia. This reaction subsided within three days after atropine was discontinued.

The patient was placed on ACTH therapy for the sympathetic ophthalmia and four days later the atropine instillations were resumed. No reaction was noted for the next seven days. At this time the dose of ACTH was reduced to 20 mgm. per day and there was a prompt return of all of the manifestations described above. These again subsided over a period of three days when the atropine was discontinued. At a later date atropine was resumed when the dose of ACTH was 40 mgm. per day and no reaction in the eye was noted.

Summary: This patient developed sensitivity to locally applied atropine during treatment for sympathetic ophthalmia. During ACTH administration atropine instillation was reinstituted without reaction until the dose of ACTH was lowered to 20 mgm. per day at which time the typical lesions reappeared. At a later time atropine was readministered when the daily dose of ACTH was 40 mgm. daily and no reaction developed.

Hypersensitivity to sulfonamides: Two patients have been treated, one of whom had a severe reaction to sulfapyridine and the other to sulfadiazine. In both, cutaneous lesions were present as well as alterations in the leucocyte count. The results suggest that ACTH may have altered the clinical course in these patients but the effects are difficult to evaluate. There was a change in the leucocyte count in both patients during therapy of a type known to be produced by the effect

of ACTH on the bone marrow function. There was no way of obtaining control observations in these cases. They are reported here to stimulate further study in instances of this type.

J. R. (JHH 517189).

This 55 year old colored laborer entered the hospital on October 31, 1949 with the chief complaint of blisters of the skin and a sore mouth. The family and past history were non-contributory. About 2 months prior to admission several "blisters" less than an inch in diameter appeared on his head. These spread over the face, neck, appendages and trunk. They occurred in small patches and there was marked pruritus. On rupture of the blebs a small red area remained. He had some fever during this period. He was seen in the Dermatological Clinic on October 10, and it was noted that there was a tendency toward grouping of the skin lesions. Irregularly outlined areas of deep pigmentation were also noted. The patient was thought to have either pemphigus or dermatitis herpetiformis, and was given 1 gm., four times daily, of sulfapyridine. On October 17 improvement was reported. However, no particulars were given. The white cell count was 7,600 with 66% polymorphonuclear cells. The patient was again seen on Oct. 31, 1949 stating that for the past week he had had nausea, chills, swelling of the feet and ankles as well as a sore mouth and throat. There were ulcerated areas on the soft palate and buccal mucous membranes covered with white exudate, and a membrane was present.

Physical Examination on Admission: Temperature 101.8°F (rectal), pulse 104, respirations 32, blood pressure 100/60. The patient was a chronically and acutely ill colored male, quite oriented and cooperative. The skin showed bullous lesions over the left elbow and left knee. Scattered over the body were flat scaly lesions which were white on the surface, but had a red and raw base varying from 1 to 4 cm. in diameter. There were scattered raw areas over the scalp and face. There was a diffuse maculo-papular, erythematous eruption over the body. The lids were edematous as were the ear lobes. The remainder of the skin was also somewhat edematous. The conjunctivae and sclerae were injected. The mucous membranes of the mouth were ulcerated and covered with a scaly white membrane. The lips were raw. There was slight generalized lymph node enlargement. The heart was not abnormal. The lungs were clear to percussion and auscultation. No organs or masses were palpable in the abdomen. Examination of the genitalia showed edema of the scrotum and raw excoriated areas over the glans. The reflexes were physiological.

Laboratory Data on Admission: STS positive. RBC 5.1 million. Hemoglobin 14.5 gm. Hematocrit 42.5. I.I. 7.5. Sedimentation rate 23 corrected. Indices normal. Smear showed 150 smudge cells per 100 intact cells. Platelets were abundant. There was some poikilocytosis. The white cell count was 725 of which 78% were large lymphocytes, 6% polymorphonuclear cells, 16% lymphocytes. Stool was guaiac negative. The urine showed 3–5 white cells, varying numbers of red cells with many granular and hyaline casts.

Course in the Hospital: The patient was obviously critically ill with a severe agranulocytosis. He was placed on penicillin 1.2 million units daily and aureomycin 4 gms. a day. The second hospital day ACTH (Armour) was started. (See Table 2.) He was given intravenous fluids as indicated. On November 1st the patient seemed somewhat improved. He was able to take some liquid feeding by mouth. The generalized erythematous rash was more prominent than it was on admission.

TABLE 2

J. R. (JHH 517189) Agranulocytosis Following Sulfapyridine Administration

DATE	TEMP. °F		WBC	GRAN.	LYMPH.	MYELOCYTE	NPN	ACTH (ARMOUR) H 6410
	Max.	Min.						
				%	%	%	*mg. %*	
10/31	105.6	104.6	725					
11/1 9 a.m.	104.4	103.6	780				35	30
5 p.m.			600					
11/2 9 a.m.	103	99.6	960				37	
2 p.m.					100			60
9:30 p.m.			1,100		98	2		
11/3 8:30 a.m.	101.8	99.4	1,300		97	3	49	
8:30 p.m.			1,600		100			60
11/4 8:30 a.m.	100.8	99	2,200		100		71	
10 p.m.			2,300					50
11/5 9 a.m.	101.4	99.6	2,900		100		103	
8 p.m.			5,700	6	83	11		50
11/6 9 a.m.	101.2	100	10,200	5	85	10		
8 p.m.			11,800	15	73	12		50
11/7 8 a.m.	102.2	100.4	13,100	33	62	5	150	

The edema of the skin had subsided somewhat, and the maculopapular rash was less prominent. On Nov. 4th the NPN began to rise and the CO_2 combining power had dropped to 17 m.eq./liter. The patient was catheterized on Nov. 5th and repeatedly thereafter until death on Nov. 8. By Nov. 7 the NPN had risen to 150. The sulfapyridine blood level on November 1 was 1 mgm.%.

Summary: This 55 year old colored laborer with dermatitis herpetiformis was treated with sulfapyridine and developed a severe reaction

with fever, dermatitis and agranulocytosis. Treatment with ACTH was followed by a rise in the total leucocyte count and the granulocyte percentage. Dosage was inadequate due to an error in standardization. The patient died in uremia. The results are not at all conclusive but are sufficiently suggestive to warrant a trial with ACTH in similar cases without such severe renal involvement.

J. M. (HLH A-74909).

This seven year old white schoolboy was transferred on December 13, 1949 from the Union Memorial Hospital because of severe stomatitis and dermatitis.

Nine months before admission, he developed otitis media for which he had received sulfonamides. Two and one-half weeks before admission he again had ear symptoms and sulfadiazine was prescribed together with prothrycin nose drops. He received the sulfonamide until the 8th of December, five days before admission. On Nov. 28th, two weeks before admission, he developed a slight rash about the groin and axilla which disappeared after taking chlortrimetron tablets. On Dec. 7th, one week before admission, he had a cough. The following evening his eyelids became swollen and droopy. Dec. 9th, five days before admission, his mouth and lips were blistered. Aureomycin was started. About 4 p.m. a rash appeared on his face, and later small blisters formed on his hands. Dec. 10th, four days before admission, there was sloughing of the mucous membranes of tongue, a rash appeared on chest and shoulders and finally over the whole body with blister formation. There was hemorrhagic fluid in some of the vesicles. The patient became progressively worse with severe ophthalmia and stomatitis. The vesicles coalesced to form large bullae. He received plasma, sulfadiazine eyedrops, and a sulfonamide ointment to his lips. He also received crystacillin. He complained of vague pain in his knees and over the soles of his feet.

Physical Examination, December 13: T 38.4°C; P 124; R 28. An acutely ill young boy who lay quietly in bed. The ear drums seemed reddened. The mucous membranes of the nose were inflamed. Mucous membranes of the lips and the proximal buccal mucous membranes were raw with considerable crusting about the lips. The tongue which could barely be seen appeared pale and denuded. There were scattered rhonchi throughout the chest. The heart was normal. Abdominal examination was unsatisfactory. There were areas below both eyes and about the lids where others had apparently tried to open the patient's eyes only to peel the skin off. On the remainder of the body was a mass of bronze-colored slightly raised areas which had the appearance of hemorrhagic blebs. There were many areas where the skin was wiped off leaving a raw surface. The surfaces of the hands were one massive bleb.

The blood sulfadiazine level was 2.4 mgm.% and there seemed little doubt that the patient had erythema multiforme bullosa secondary to this drug. New bullae appeared on the first day. The eosinophil count was 88 per cu. mm. Total white cell count was 2,300 with 73% granulocytes, 24% lymphocytes and 2% monocytes.

Administration of ACTH (Searle) 30 mgm. every six hours was begun on December 14. No new bullae formed. The temperature promptly returned to normal, as did the pulse rate. The eosinophil count dropped to 11 per cu. mm. The lesions showed considerable drying over the next few days and new skin began to form. By December 17 the patient was able to open his eyes. The white cell count rose to 11,400 on December 16 with 4% juvenile cells, 88% mature granulocytes, 7% lymphocytes, and 1% monocytes.

December 21, the ACTH was stopped. The following day the temperature rose to 39°C. The blood culture showed a moderate growth of hemolytic staphylococcus aureus. Chloramphenicol therapy was begun. From this time on healing was very slow and was not complete at the time of his discharge on January 25.

Summary: This 7 year old boy had a severe bullous dermatitis with leucopenia secondary to the administration of sulfadiazine. During seven days of treatment with ACTH there was more rapid healing of the skin which again slowed its pace when the drug was stopped. The white cell count reached normal on the third day of therapy.

Reaction to 3-Hydroxy-2-phenyl Cinchoninic Acid: This drug has been used during the past year in the treatment of acute rheumatic fever and its effects have been explored in a variety of other diseases (9). Patients who are exposed to sunlight while taking this substance may develop a photosensitivity reaction which subsides promptly when exposure is ended. In addition, febrile reactions have been observed in two patients while in the hospital. One of these is described below. Whether or not ACTH influenced the drug reaction in this case is problematical, but the implications of these observations are sufficiently provocative to warrant recording them.

K. L. (JHH 464514).

This patient was a 36 year old white male who was admitted on Jan. 4, 1950 with chronic lupus erythematosus involving the skin of the arms, legs, and upper trunk. On Jan. 25 he was begun on treatment with 3-hydroxy-2-phenyl cinchoninic acid (HPC) 20 mgm./Kg. each day (1.7 gms.). During the next seven days he had a slight and questionable improvement in the cutaneous lesions. On the eighth day, his temperature rose to 101.4°F (rectal), and he complained of severe malaise, conjunctivitis and coryza. He later had a shaking chill and developed a diffuse erythema most marked over the face and upper trunk. The HPC was stopped, following which the symptoms disappeared and the temperature returned to normal.

Six days later the patient was given 200 mgm. of HPC by mouth and the following day 400 mgm. There was a rise in temperature about 20 hours after the first dose with the same accompanying signs and symptoms but of a milder degree.

On Feb. 12 he received 1 gm. of HPC and 6½ hours later had a rise in temperature to 101.6 and severe manifestations as before.

Feb. 19 and 20 he received ACTH 25 mgm. every 6 hours (Armour Standard). On Feb. 21 he received 80 mgm. but there was no appreciable fall in the circulating eosinophil count. From 9 to 11 a.m. on Feb. 22 he was given 1.0 gm. of HPC. At 5:30 p.m. he developed flushing of the skin, conjunctival injection and coryza. At 10 p.m. he had a severe throbbing headache, a violacious hue of the skin of the face and marked periorbital edema. At 2 a.m. there was marked coryza and the temperature had risen to 102.2. At 9 a.m. the following morning the temperature was 103.4, the face was scarlet, and the wrists and hands were swollen. At 12 noon the ACTH dosage was increased to 50 mgm. every 6 hours and four hours later the eosinophil count had fallen from 88 to 33. At noon the HPC blood concentration was 3.7 mgm.%. At 8 a.m. the following morning the temperature was normal, the edema had largely subsided and the patient felt quite well. The eosinophil count was 11. Beginning at 11 a.m. he was given 500 mgm. of HPC over a two hour period. This was followed by no reaction at all.

The ACTH dosage was gradually tapered off during the next 12 days. Every 48 hours he was challenged with 600 mgm. of HPC by mouth for a total of seven times but had no further evidence of hypersensitivity to the drug. The last challenge was carried out seven days after the final dose of ACTH.

Summary: This 36 year old man with lupus erythematosus of the skin developed a hypersensitivity reaction to HPC characterized by fever, headache, erythema of the skin, periorbital edema, conjunctivitis and marked coryza. ACTH in doses of 100 mgm. a day failed to block the reaction to 1.0 gm. of HPC orally but when the ACTH dosage was raised to 200 mgm. there was a fall in temperature and rapid subsidence of the reaction. The patient was challenged with HPC on seven occasions without reaction, the last seven days after withdrawal of ACTH.

Hypersensitivity to Acetylsalicylic Acid: It has been known for many years that patients with bronchial asthma may be sensitive to this drug with the development of a severe attack following the ingestion of as little as 0.3 gm. Death has been reported after 0.6 gm. (10). This type of sensitivity tends to occur in patients with the intrinsic type of asthma who have had chronic infection of the sinuses or respiratory tract.

The following case report describes the observations made on a patient of this type who was challenged with acetylsalicylic acid during the administration of ACTH. The results are by no means con-

clusive but they form the basis for certain speculations and a focal point for further studies.

J. F. (JHH 528483).

This 28 year old white male entered the hospital on February 8, 1950, for treatment of intractable bronchial asthma.

He first noticed a cough with tightness in his chest in 1942 while in South Africa. In January, 1943, he had his first severe attack of asthma, evidently of an intrinsic type, and had had constant difficulty for three years prior to the present admission.

Physical examination at the time of admission showed normal temperature, pulse rate and blood pressure. The chest was emphysematous in shape. The percussion note was hyperresonant throughout and numerous sibilant and sonorous rales were heard over both lung fields. Expiration was greatly prolonged and the breath sounds were very harsh. Numerous large nasal polyps were present, and the sinuses transilluminated poorly.

Of most interest is the history in regard to aspirin sensitivity. During childhood and as late as the early months of 1942 the patient had been able to take this drug without any ill-effects. In October 1942, he had an upper respiration infection accompanied by a feeling of tightness in the chest. He took 0.6 gm. of aspirin and developed shortness of breath within a few moments which lasted for an hour. In January, 1943, following a dental extraction he took two "anacin" tablets. Two hours later he developed his first very severe attack of asthma, and has had constant difficulty with asthma since that time. In December, 1943, he was given a tablet said to be quinine. Ten minutes later he developed extreme dyspnoea and after 20 minutes was comatose. He began to improve after vigorous anti-asthmatic therapy for 48 hours but had severe symptoms for a week. In May, 1944, he took one capsule of a patent medicine for asthma which contained aspirin and quinine. Within a few minutes he developed an asthmatic attack which became so severe that he was comatose after 90 minutes. He remained comatose for 24 hours and his asthma remained so severe that he had to remain in hospital for the succeeding two months. Finally, in June, 1945, he was given one "APC" tablet by mistake. One hour later he developed severe asthma which persisted for two days.

The patient was treated with ACTH and after his asthma had been completely relieved consented to take aspirin while still under ACTH therapy. The details of these experiments are outlined in Chart 1.

He was challenged with 130 mgm. of acetylsalicylic acid on February 25 when he was receiving 35 mgm. of ACTH (Armour standard) every six hours. 100 minutes later he developed slight tightness in the chest and a few wheezes were heard throughout both lung fields. At 130 minutes he had moderately severe asthma which was readily controlled with 0.5 gm. of aminophyllin intravenously. The following day he had a much milder transient attack of asthma about 150 minutes after the administration of 64 mgm. of aspirin. Further challenges with 32 mgm. of the drug were made over the next week as the dosage of ACTH was tapered

and finally stopped on March 4. The final administration of aspirin (80 mgm.) was ten days later and no asthma was precipitated.

These results are difficult to interpret. The asthma provoked by aspirin while he was receiving ACTH was much milder and of far shorter duration than in any of his previous episodes which followed this drug. However, the administration of 80 mgm. of aspirin after ACTH was discontinued did not precipitate an attack

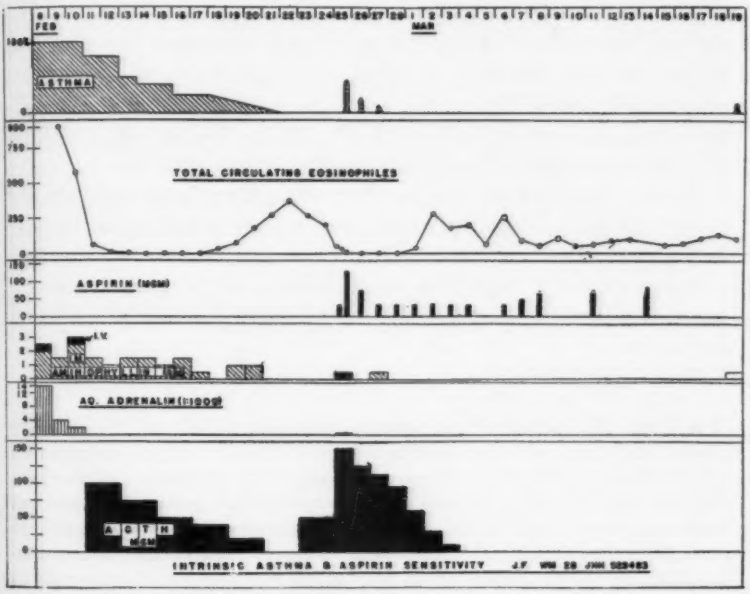

CHART 1. J. F. (JHH 528483) Bronchial asthma with hypersensitivity to acetyl salicylic acid during treatment with ACTH.

whereas 64 mgm. had previously done so while he was on large doses of ACTH. It seems possible that the repeated administration of small amounts of aspirin in the intervening period between these two tests may have desensitized him to some degree. This point is of importance and should be further explored.

Summary: This patient with severe intractable asthma of the intrinsic type was sensitive to acetylsalicylic acid. The administration of large doses of ACTH did not prevent the development of a mild attack of asthma following the oral administration of 130 mgm. of

aspirin. 32 mgm. did not produce asthma while 64 mgm. induced a milder more transient attack. After ACTH was stopped 80 mgm. of aspirin precipitated no asthma. It is possible that the repeated administration of small doses of this drug has resulted in partial desensitization.

Paroxysmal (cold) Hemoglobinuria with Urticaria: The hemolytic system of paroxysmal (cold) hemoglobinuria requires both an hemolysin and complement. As ACTH apparently influences the effects of antigen-antibody reactions it appeared of interest to study the possible activity of ACTH on this hemolytic system. Therefore, the following experiments were done by Dr. Philip Wagley on a patient who also developed urticarial lesions after exposure to cold.

Serum and cells were obtained from the patient's blood previously drawn into syringes and tubes warmed to body temperature. Reagin, cold agglutinin and cold hemolysin titers were determined by standard techniques (11–13) employing serial dilutions of the patient's serum. Serum complement activity was titered with previously sensitized sheep cells.

M. E. (JHH 414118).

A 33 year old Negress had been admitted previously in 1947 with the chief complaint of dark urine following exposure to cold. The family and past histories were non-contributory. The present illness apparently began five years prior to admission with periodic attacks of swelling of the eyelids, lips, periorbital tissues and fingers on exposure to cold. This swelling was associated with itching of the affected parts. Both the swelling and itching would disappear usually within twenty minutes when the patient became warm. Such exposure to cold would occasionally be associated with mild transient abdominal cramps. There was no nausea or vomiting. Four years prior to the present admission the patient noticed that her urine became red, dark, and almost black after she was exposed to cold. The urine would remain dark for only four to six hours. The patient stated that her eyes had been yellow occasionally during winter months. Drinking ice water would result in a tight sensation in her throat. No dark urine had been noted following consumption of cold drink or food. The physical examination was essentially negative. The serologic test for syphilis was positive. The Donath-Landsteiner test was positive. The clinical diagnosis was syphilis associated with paroxysmal (cold) hemoglobinuria and angioneurotic edema following exposure to cold.

Reagin, cold agglutinin, cold hemolysin and complement activity titers were determined prior to ACTH treatment as recorded in Table 3.

The first experiment was done before treatment and after a fasting state of 10 hours. An indwelling catheter was placed in the patient's

TABLE 3

M. E. (JHH 414118) Paroxysmal (Cold) Hemoglobinuria. Effect of ACTH on Cold Hemolysin, Cold Agglutinin, Complement, and Reagin Titers

COLD HEMOLYSIN TITER	1/1	1/2	1/4	1/8	1/16	1/32
11-2-49 (Before ACTH)	++++	++++	+++	++	tr	0
11-5-49 (After 2 days Rx)	++++	++++	++++	+	tr	0
11-7-49 (After 5 days Rx)	++++	+++	++	+	tr	0

COLD AGGLUTININ TITER	1/2	1/4	1/8	1/16	1/32	1/64	1/128	1/256
11-2-49 (Before ACTH)	hem	hem ++	++++	++++	+++	+	0	0
11-5-49 (After 2 days Rx)	hem ++++	++++	++++	+++	++	+	?	0
11-7-49 (After 5 days Rx)	hem ++++	++++	++++	+++	+++	+	0	0

COMPLEMENT TITER	1/2	1/4	1/8	1/16	1/32	1/64	1/128	1/256	1/512
11-2-49 (Before ACTH)	++++	++++	++++	+++	+++	++	+	tr	0
11-5-49 (After 2 days Rx)	++++	++++	+++	+++	++	+	±	tr	0
11-7-49 (After 5 days Rx)	++++	+++	+++	+++	++	+	tr	0	0

REAGIN TITER	
11-2-49 (Before ACTH)	8 units
11-5-49 (After 2 days Rx)	8 units
11-7-49 (After 5 days Rx)	8 units

bladder for the duration of the four hour study. The patient's right foot was immersed in ice and water for 20 minutes. The temperature of the water bath was less than 3°C. The foot was then removed from

the ice-water bath and allowed to warm at room temperature. Five minutes after chilling hives appeared over the dorsum of the foot and extended up to the level of the malleoli. They were detectable for about 20 minutes. There was itching in the same area. The patient was nauseated but did not vomit. The urine remained yellow, clear, and guaiac negative until an hour and 15 minutes after chilling. The urine then became progressively darker and red and remained so for over an hour. Though it contained no microscopically detectable red blood cells it was strongly positive to guaiac. Prior to chilling of the foot 2 cc. of blood was obtained in a siliconed syringe and tube and immediately centrifuged. The supernatant plasma was pale yellow. Two cc. of blood obtained in an identical manner 40 minutes following removal of the foot from the ice-water bath contained in the plasma more than 200 mgm. hemoglobin per 100 cc.

The patient was started on therapy with ACTH (Armour Lot # 7010). After receiving a total of 87 mgm., administered in divided doses every 6 hours, and 2 hours after the last i.m. injection of 12.5 mgm., blood was again drawn for determination of reagin, cold agglutinin, cold hemolysin and complement titer. On the fifth and last day of therapy and after a total dosage of 450 mgm., two hours and 15 minutes after the last i.m. injection of 12.5 mgm. of ACTH, the above studies were repeated (see Table 3). At the time of these determinations the eosinophil counts were 0. Immediately before ACTH treatment the counts had been 55 per c. mm. There was no significant change in any titer in serum removed before therapy, 48 hours after beginning treatment or at the end of the period of observation, after 5 days of therapy.

Again on the 5th and last day of therapy (total dosage 450 mgm.) and 135 minutes after the last injection of 12.5 mgm. of ACTH the patient was catheterized and her right foot immersed in ice and water for 20 minutes. Prior to chilling the urine was yellow, clear and guaiac negative. Plasma from blood drawn into siliconed syringe and tube was clear yellow. No hives or itching developed after chilling for 20 minutes. The patient was slightly nauseated. Forty minutes after the chilling blood again drawn into a siliconed syringe and tube showed a red supernatant plasma that contained more than 200 mgm. hemoglobin per 100 cc. Between 1 and 2 hours after chilling the urine became dark

and reddish-brown. Though no red blood cells were demonstrable microscopically it was strongly positive to guaiac.

One-tenth of a cc. of histamine base solution with a concentration of 5 mgm. per cc. was injected intracutaneously into the volar surface of the right arm immediately after the last experiment. Four minutes later a pseudopod 4 cm. long had developed, thus demonstrating the patient could still react to histamine base even though the usual hives and itching had not developed after the exposure to cold.

Summary: After the administration of 450 mgm. ACTH in a period of 5 days to a patient with paroxysmal (cold) hemoglobinuria titers of cold agglutinin, cold hemolysin, complement, or reagin did not change significantly. Chilling the foot of the patient both before and after such therapy produced hemoglobinemia and hemoglobinuria. However, hives and itching of the skin of the chilled foot did not appear after the ACTH injections. At that time the patient reacted to histamine injected intracutaneously with the formation of pseudopodia.

DISCUSSION

It was hoped that an investigation of the clinical effects of ACTH and cortisone on drug hypersensitivity reactions would be profitable not only from the practical but also the theoretical viewpoint. There is some reason to believe that a better understanding of drug allergy might contribute not only to a better understanding of other allergic phenomena, but also of the part that allergy plays in the pathogenesis of other diseases such as the infections and those involving the mesenchymal tissues.

The present report gives in detail the clinical results in a variety of situations. There has been no doubt in the minds of the observers that in most of the instances ACTH had a profound effect on the course of the sensitivity reaction. The patients with exfoliative dermatitis were critically ill at the time treatment was begun and made a dramatic recovery. In the patients with a condition like serum-disease resulting from penicillin the recurrence of urticaria 5–14 days after cessation of ACTH therapy serves to show that disappearance of the sensitivity manifestations was the result of increased adrenal activity and not simply a coincidental and spontaneous recovery. Perhaps, the most striking demonstration was the almost complete abolition of the violent

reaction to patch test with atropine. These cases have been presented in detail for the benefit of those who will have the opportunity to gain further experience in this particular field. The results thus far are limited and no final conclusions can be drawn from them.

These studies were stimulated by the observations of Rich and Gregory as pointed out in the introduction. Berthrong, Rich and Griffith (14) have now studied the effect of ACTH on the cardiovascular lesions evidenced in rabbits by the administration of horse serum. Forty rabbits were sensitized with horse serum in the manner known to produce the periarteritis nodosa and cardiac inflammatory lesions. Half of the animals were treated with ACTH; the remainder serving as controls. Well-marked vascular or cardiac lesions or both were found in 18 of the 20 untreated controls, and in only 5 of the 20 animals treated with ACTH.

When one considers this evidence that the 11, 17 oxysteroids in some way block allergic reaction to drugs and foreign protein, hypersensitivity reactions due to any antigenic effect of ACTH itself would not be expected to occur if enough was being given to stimulate the adrenal cortex at the necessary level. This prediction is borne out by the fact that signs and symptoms ordinarily encountered as manifestations of drug hypersensitivity have been rarely observed during ACTH administration. We have seen the development of urticaria in a patient during cortisone therapy for disseminated lupus erythematosus. The sensitivity was apparently due to chloromycetin and its clinical appearance was evidently suppressed until the dosage of cortisone reached a low level.

The mechanisms which are responsible for the beneficial effects of ACTH and cortisone on the hypersensitivity manifestations are not clear. It is stated that the flare-and-wheal reaction, of which giant urticaria has been assumed to be a dramatic example, is the product of three steps: first, the release of the H-substance of Lewis, probably histamine, owing to the stimulus of a local antigen-antibody reaction; or to mechanical cellular injury, and in consequence the release of histamine. The second step is the flare, probably an arteriolar dilatation, the result of an axon reflex. The third step, the central blanched wheal, resulting from more severe damage to capillary endothelium by continued presence of the H-substance. In a number of instances intracutaneous injections of histamine have been given to individuals

being treated for a wide variety of diseases with ACTH. In no instance has there been any evidence that the local cutaneous reaction to injected histamine has been suppressed. When curare, among other substances, is injected intradermally a wheal and flare develops which has been thought also to be the release of naturally occurring histamine at the site of injection. This reaction is not blocked either in patients receiving large doses of ACTH (15).

Also of considerable interest is the experiment on the patient with paroxysmal (cold) hemoglobinuria who developed urticaria of the foot following chilling. During the administration of ACTH the development of the urticaria was blocked but the antigen-antibody reaction with hemolysis of erythrocytes was not interfered with. Also in this patient the cutaneous wheal-and-flare following the injection of histamine was not altered.

The studies conducted by Mirick (16) on these patients in respect to the formation of antibodies to pneumococcal polysaccharides are of interest. He found that while ACTH was being given antibodies formed at the usual rate and in the usual quantities. If at the proper time interval, however, a Francis test was done, the cutaneous reaction was, in most instances, blocked if the patient was receiving ACTH. These results suggest that ACTH acts by altering the abnormal tissue reaction that follows the union of antigen and antibody. There is as yet, however, far too little knowledge to gain any real understanding as to the mechanism of these effects.

As Sherman (6) points out numerous investigators have tried to desensitize patients with a drug allergy by gradually increasing doses of the causative drug. He states that although the procedure has frequently proven effective in the case of heterologous sera and other proteins, the evidence for desensitization as far as non-protein agents are concerned is less convincing. Sherman feels that in the present state of knowledge, the theoretical danger of attempted oral desensitization outweighs any evidence of its practical value. In this regard the experiences recorded in this communication are of interest. The interpretation of the results is difficult. The last exhibition of the specific drugs after the cessation of ACTH administration was perhaps not long enough to know whether the response was blocked by a high level of adrenal activity or whether desensitization had occurred as a result of the repeated administration of the acetylsalicylic acid in the one

instance and the 3-hydroxy-2-phenyl cinchoninic acid in the other. Further studies of this type are obviously indicated from several points of view. One would like to know more about the quantitative aspects of this blocking action of ACTH on the tissue reaction to drug hypersensitivity and of great practical importance is the extent to which ACTH will aid the techniques of desensitization throughout the field of allergy.

The response of the leucocytes in the cases with sulfonamide hypersensitivity are of interest. Experimental studies have amply demonstrated that both ACTH and cortisone produce a striking neutrophilia. This finding has been generally observed in the various studies in man. It is difficult to tell in the cases reported in this paper whether the change in the leucocytes was spontaneous or actually the result of the ACTH therapy. In both instances it occurred on the third day and at a time when other evidences of clinical improvement were slight or absent. The results certainly indicate further exploration of the effect of ACTH and cortisone in cases of this type.

Caldwell and his coworkers (17) have recently reported a case of agranulocytosis due to a sulfonamide treated with cortisone. Treatment was first instituted with pentonucleotide, antibiotics, blood transfusions and liver extract. At the time cortisone was started there was evidence of early neutrophylic regeneration. The white cell count rose to 25,400 on the sixth day of treatment. These suggestive results need further confirmation but offer promising possibilities in the treatment of this serious abnormality.

SUMMARY

1. The effect of ACTH and cortisone on the various clinical manifestations of hypersensitivity to iodine, sulfonamides, penicillin, acetylsalicylic acid, hydroxy-phenyl-cinchoninic acid and atropine have been described. Studies before and during the administration of ACTH have been carried out on a case of paroxysmal (cold) hemoglobinuria in whom urticaria appeared after chilling.

2. The results of the readministration of penicillin, atropine, acetylsalicylic acid, and hydroxy-phenyl-cinchoninic acid to sensitive patients during ACTH administration have been outlined.

3. The effects of ACTH on the hemotological picture in two patients

with leucopenia following the administration of sulfonamides have been observed.

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THE EFFECT OF ADRENOCORTICOTROPIC HORMONE (ACTH) AND CORTISONE ON THE COURSE OF CHRONIC BRONCHIAL ASTHMA

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INTRODUCTION

In an earlier report the dramatic relief of chronic intractable bronchial asthma during the administration of ACTH was described (1). During the past ten months further observations have been made concerning the immediate response to the administration of ACTH and cortisone, the most effective dosage schedules, the duration of the remissions, and the response to subsequent administration of these hormones after relapse. In addition, a control study designed by Dr. Margaret Merrell of the Department of Biostatistics has been carried out in order to evaluate the influence of psychogenic and environmental factors on these observations. The present communication describes the effect of ACTH in 23 patients with chronic intractable asthma in the majority of whom there occurred complete remission of all signs and symptoms of the disease for periods up to ten months. Cortisone has been given to five similar patients with less improvement noted from exhibition of this hormone in the doses used.

MATERIAL AND METHODS

In order to mimimize the influence of psychogenic and environmental factors only patients who had had constant asthma for at least two months were included in the study. All patients had a severe chronic form of the disease and had received no satisfactory relief from any other type of treatment, including symptomatic measures and desensitization. It can be seen from the tables that the series was about evenly divided between males and females. The ages ranged from 26 to 75 years and the duration of the asthma from 6 months to 45 years. All patients were considered to have intrinsic asthma and in four one or more extrinsic factors were thought to play a rôle.

Each day that the patients were under observation an assessment of their clinical status was made using both subjective and objective criteria. The most useful subjective manifestations were degree of dyspnoea, feeling of tightness or weight on the chest, effort in breathing, and capacity for exertion. Among the objective data recorded were ability to lie flat in bed, respiratory rate at rest and after exertion when possible, use of accessory muscles of respiration, character and distribution of auscultatory signs, amount and character of the sputum, vital capacity, and spirometric tracings.

In evaluating benefit which resulted from the ACTH or cortisone, subjective relief was considered complete when, without adjuvant treatment, the patient no longer experienced any sense of respiratory discomfort, even to the feeling of weight on the chest. The latter symptom, occurring in the early morning on waking, was usually the last to disappear. Remission from asthma was considered objectively complete when musical and other rales had been inaudible by stethoscopic examination for 48 hours, even after mild exertion. In those patients who were tested spirometrically, the return of the expiratory phase of respiration to the normal pattern coincided with the patients' statement of subjective relief.

In the special control group only those patients were used who had had asthma for at least five years, with no freedom from symptoms for at least two months despite vigorous symptomatic therapy. Any obvious infection in the lower respiratory tract was cause for exclusion from the group, as was the possibility that any of the symptoms might be of cardiac origin. Each patient had to express complete willingness to be hospitalized for at least a month and to cooperate in any procedures indicated in the study. The patients agreed to stop all adjuvant drugs but one (usually they chose a spray or aminophylline suppositories) during the experimental period, and even this one was to be used only with concurrence of the doctor. In an emergency the physician conducting the study, and who was the only person knowing whether placebos or ACTH was being given, was to decide the need of any additional treatment.

The drug being tested (ACTH or cortisone) and the placebo were indistinguishable, the ACTH control being a standard solution of pitressin in saline made up in old ACTH bottles; the cortisone control

was a suspension of cholesterol, kindly furnished by Merck and Company. The patients were all told they were to receive ACTH or cortisone, and together with the nurses and attendants were all unaware that a control study was being carried out. Each day independent observations were made by two physicians who did not know the identity of the material being used; and these observers did not have access to the patient's weight chart, eosinophil chart or results of other collateral studies. Standard courses of treatment were arbitrarily decided upon. In the case of ACTH, 100 mgm., 75 mgm., 50 mgm., 40 mgm. and 20 mgm. per day were given for two day periods, a total period of ten days' administration of the drug. Cortisone was given 200 mgm. the first day and 100 mgm. daily for the next seven days. The ACTH and cortisone were both administered intramuscularly, one-fourth the daily dose being given every six hours.

The patients were assigned to two groups in random fashion. A list giving an order of assignment was prepared by Dr. Merrell, and was available only to the one physician who knew the identity of the drug being given to the patient. The placebo was administered for five or eight days, either before or after the course of the active agents. Thus, a given patient might receive placebos for five days, followed by ten days of ACTH, ten days of ACTH followed by placebo, placebo for five days followed by cortisone or vice versa.

The assessment of clinical status was made after five, eight and fifteen days in each instance.

Before administration of either ACTH or cortisone to any patient the following studies were carried out: 1) eosinophil counts (blood and sputum), 2) measurement of daily sputum volume, 3) determination of vital capacity during the maximal relief obtained by the most effective symptomatic therapy (epinephrine or aminophylline), 4) hematocrit, sedimentation rate, white cell and differential counts, 5) blood non-protein nitrogen and sugar, serum chloride and bicarbonate concentrations, 6) daily blood pressure recording, 7) morning weight with empty bladder, 8) electrocardiogram and determination of venous pressure.

After treatment was begun, blood pressure, vital capacity and sputum volume were recorded daily. Eosinophil counts were taken each morning, four hours after the morning injection, until they reached

TABLE 1

Age, Sex and Duration of Asthma in the Patients Treated for the First Time with ACTH

	CASE	HISTORY NO.	SEX	AGE	ASTHMA		ACTH			EOSINOPHILES				COMPLETE REMISSION		REMISSION
					Years	Type	Total	Starting dose	Days	Before RX	Minimum after RX	Fall %	Fall On day	On day	Duration	
							mgm.	*per day*							*days*	%
1	R. M.	511025	F	40	18	E & I	440	50	12	1100	22	98	5	4	86	100
2	H. N.	231977	M	63	18	I	578	50	16	1050	66	94	5	7	105	100
3	E. M.	512303	M	34	2	E & I	732	20	21	484	11	97	5	7	263+	100
4	W. S.	170250	M	38	12	I	338	50	11	821	66	92	2	2	25	100
5	F. L.	434666	F	54	27	I	527	100	12	360	66	72	5	7	60	100
6	J. B.	170223	F	44	8	I	477	80	10	462	11	98	2	3	70	100
7	D. H.	336367	M	41	5	I	798	140	10	300	33	89	7	4	40	100
8	B. M.	200493	F	75	12	I	570	100	10	286	0	100	2	3	116	100
9	O. Z.	358563	M	57	2	I	193	25	11	1056	88	92	4	5	7	100
10	M. G.	528824	M	57	½	I	600	100	10	1496	0	100	2	8	75+	100
11	J. F.	528483	M	28	6	I	1248	100	18	899	6	99	3	11	15	100
12	M. H.	527856	F	46	9	I	570	100	10	550	0	100	7	4	100+	100
13	H. W.	532987	M	55	12	I	240	50	6	528	286	46	3	5	51+	100
14	B. de S.	530526	M	53	1	I	285	85	4	858	77	91	4	3	3	100
15	M. S.	435221	F	26	4	I	786	80	14	605	154	75	5	4	14+	100
16	N. B.	100080	F	26	23	I	826	100	16	524	67	87	5	None		95
17	H. S.	512338	M	44	1½	I	232	50	9	921	715	23	3	None		40
18	L. I.		F	65	45	E & I	190	25	8	2800	160	94	6	None		50
19	J. G.	535594	F	56	26	E & I	695	100	13	572	11	98	2	None		50

In type of asthma, I signifies intrinsic, E that extrinsic factors—such as inhalants—were thought to play a role. Maximal and minimal blood eosinophile counts are given and the day on which the fall was greatest. The day after ACTH administration on which all symptoms and signs of asthma were first absent is listed as day of complete remission. Duration of remission in most instances was determined from the patients' own evaluation, usually the time when spray or suppository therapy became necessary again for comfort.

minimal levels; thereafter counts were made at 2-day intervals until discharge. Other blood counts and chemical determinations were carried out twice weekly. Most of the patients kept a daily biographical record of their course while in the hospital.

The ACTH used was ACTH Armour, the doses listed are in milligrams of Armour Standard, and the daily dose was always divided into four equal parts given intramuscularly at six hour intervals. The daily dose of cortisone acetate (Merck) is also expressed in milligrams and this hormone was administered in a similar manner. In those patients not in the control series the dosage schedules of ACTH and cortisone varied widely. In several instances dosage was higher or lower than intended, owing to error in assay of the ACTH. In most patients the starting dose was 50 to 100 mgm. per day, and after one to three days on this schedule the dose was gradually lowered. To one patient, critically ill in status asthmaticus, it was deemed wise to give a larger initial dose (100 mgm. in first six hours) to be certain of obtaining the earliest possible maximal effect. In another instance 20 mgm. per day was given at the start in an effort to determine minimal effective dosage.

The total amount of ACTH given in the initial course of treatment in these patients varied from 190 to 1248 mgm., with an average of 423 mgm. The duration of therapy varied from four to twenty-one days with an average of 11.6 days. The patient receiving the largest total dosage (Case 11, Table 1) was sensitive to acetyl salicylic acid and after his asthma had cleared ACTH was continued at a high dosage for greater safety while he was being challenged with aspirin. The patient receiving the longest period of treatment (21 days in Case 3, Table 1) started at a low daily dose which was gradually raised in an effort to determine the minimal level at which response occurred. The treatment schedules for cortisone are presented in Table 3.

RESULTS

Fifteen of the nineteen patients (Table 1) achieved subjective and objective remissions of their asthma while taking ACTH. The four who did not obtain complete freedom from asthma (the last four in Table 1) experienced 50 per cent or more reduction in severity, as judged by themselves and the observers.

symptoms and signs of asthma were first absent is listed as day of complete remission. Duration of remission in most instances was determined from the patients' own evaluation, usually the time when spray or suppository therapy became necessary again for comfort.

There was noticeable symptomatic improvement, both to patient and physicians, often within four hours, always within thirty-six. The rapidity with which complete relief was attained varied; in some instances adjuvant therapy, which served as an excellent guide to the subjective status, was no longer necessary after a few hours; in others, such medication could not be comfortably abandoned for nearly a week. In this group, early improvement did not necessarily indicate eventual freedom from asthma, though other factors may have played a rôle in those who did not achieve complete remission, as will be mentioned later.

In attempting to evaluate the effect of the dosage level on the completeness of the freedom from asthma, the variability of the disease from patient to patient must be considered despite the fact that all but two of these individuals had severe constant asthma and were free of complicating pulmonary infection. In reviewing those patients (the last four in Table 1) who failed to obtain complete remission, it is noted that patients #17 and #18 received very small doses. This was unintentional and due to an error in assay of the ACTH not discovered until later However, patient #9, who because of the error in assay, received no greater dose, obtained complete relief on the fifth day; and patient #3, who was purposely begun on 20 mgm. per day and the dose increased to 30 mgm. on the sixth day, experienced a total remission of asthma on the seventh day. In order to observe the effects on nasal polyps, the dose was increased further and later was gradually reduced. The total period of treatment was 21 days. He has had no asthma during the succeeding ten months, despite severe upper respiratory infections, although the polypi have recurred. Furthermore, cases #16 and 19 were begun on 100 mgm. ACTH per day and received total doses considerably in excess of that given to many patients who achieved complete and lasting remissions. Patient #16 was in her sixth and seventh months of pregnancy while the ACTH was given. She experienced prompt relief and was free of all subjective manifestations by the fifth day, but the auscultatory signs never entirely disappeared. Two days after ACTH was stopped, coincident with an upper respiratory infection, the asthma recurred in sufficient severity to require epinephrine. She continued to have asthma with approximately 50 per cent of its previous severity until delivery. Since then asthma has been very mild. Similar postpartum alleviation followed two of her four

previous pregnancies, though after two other deliveries her asthma became greatly exaggerated.

Patient # 19 had had asthma for more than 25 years and had always noted a marked exaggeration in damp and humid weather. During most of the time she was receiving ACTH, the weather was extremely hot and humid, and the patient herself stated that previous experience made her certain that she would have required almost constant injections and sprays had it not been for the beneficial action of ACTH.

The duration of the complete remissions from asthma has varied from three days up to ten months. The average length of the freedom from any difficulty has been 68 days. The patients with the longest remissions after ACTH were # 1, 2, 3 and 8 in Table 1, the duration of complete freedom being 86, 105, 263 and 116 days, respectively. The patients whose remissions were shortest were # 4, 9, 11 and 14, with freedom for only 25, 7, 15 and 3 days, respectively. Comparison of these two groups discloses that a patient in the short remission group received the largest total dose and was treated for the longest period, that two of the group with short remissions began on 100 mgm. per day, whereas only one patient with a long remission began on so high a dose. However, the patient with the shortest remission of all was treated with the smallest dose over the fewest days. It is worthy of note that in no instance thus far has the severity of asthma in the relapse been as great as prior to administration of ACTH.

It seems likely that in two of the failures, larger doses of ACTH would have effected complete asthmatic remissions. However, one patient refused to submit to another trial with ACTH, owing to unpleasant side effects experienced in the first course even with the small dose, and the other patient has moved to a distant part of the country so that the effects of a second course of ACTH could not be observed.

The response to second and third courses of ACTH

Seven of the patients have received more than one course of ACTH. All of these had responded to their first course with complete remissions. Each likewise responded to the subsequent courses with disappearance of all symptoms and signs of asthma. Table 2 depicts the dosage schedule, promptness and duration of remissions with *each* of their courses of ACTH.

The first patient's second course of ACTH was much briefer than

TABLE 2

Dosage and Results After the First and Subsequent Courses of ACTH

CASE	HISTORY NO.	COURSE NO.	ACTH			REMISSION			INTERVAL BETWEEN COURSES	EOSINOPHILES			
			Total	Starting dose/day	Days	%	On day	Duration		Before RX	Min. after	Fall	On day
			mg.	*mg.*					*days*			%	
1 O. Z.	358563	1	193	25	11	100	5	7	...	1056	88	92	4
		2	200	50	4	100	3	80	133	363	0	100	3
2 J. B.	170223	1	477	80	10	100	3	70	...	462	11	98	2
		2	200	50	4	100	2	14	105	561	0	100	4
		3	288		5¼	100	3	30*	48	517	0	100	3
	UMH												
3 H. N.	14912	1	578	50	16	100	7	105	...	1050	66	94	5
	231977	2	570	100	10	100	9	55	172	275	55	80	5
		3	950	50	17	100	16	21+	44	2079	33	99	4
4 D. H.	336367	1	798	140	10	100	4	40	...	300	33	89	7
		2	225	50	5	100	5	55	55	132	220	0	—
5 R. M.	511025	1	440	50	12	100	4	86	...	1100	22	98	5
		2	200	40	5	100	4	11	224	1056	0	100	3
6 J. F.	528483	1	1248	100	18	100	11	15	...	899	6	99	3
		2	1641	100	26	100	15	14+	63	781	0	100	15
7 B. de S.	530526	1	285	85	4	100	3	3	...	858	77	91	4
		2	210	40	5¼	100	3	3	6	1331	163	88	3

* This patient continued to receive ACTH twice weekly (see text).

the previous one, the daily initial dose having been doubled. Thus, he received in four days (50 mgm. per day) as much ACTH as he had received in 11 days previously. The response was more rapid, complete remission occurred within three days, and the duration of the second remission was 80 days as compared with 7 days following the first course. The interval between the two courses was 133 days; so that the patient had had asthma for 126 days prior to his second administration of ACTH. It should be noted, however, that the asthma was only 75 per cent as severe as when the first course was begun.

In the second case the second course of ACTH was begun 105 days after termination of the first, when mild asthma had been present (estimated at 50%) for 33 days. In the second period of treatment the patient received 50 mgm. ACTH per day (as opposed to 80 mgm. initial dose in the first course), but with a *total* dose only two-fifths of the first and for four days total treatment rather than ten. Remission was equally prompt but lasted only two weeks. Then, after asthma of only mild severity had been present for six weeks, a third course of ACTH was given, identical with the second except that 50 mgm. was given daily for six days instead of four. Prompt remission again resulted, and the patient was then given 80 mgm. per day in *two* doses on two days out of each week for two weeks, then 40 mgm. per day in two doses twice each week. Asthma recurred on the twenty-ninth day.

Patient #3 had three courses of ACTH. His first two courses were of approximately the same *total* dosage, but initial dosage was smaller with the first course and injections were given over 16 days as compared with ten. The former resulted in a complete remission lasting 105 days, the latter only 35 days. His third course of ACTH was complicated by the development of pneumococcal pneumonia on the third day. Penicillin promptly overcame this infection and treatment with ACTH was not interrupted. However, he continued to have slight oppression in breathing and a few expiratory wheezes were heard until the seventeenth day of treatment. By the time the pneumonia developed, his asthma had cleared sufficiently so that antiasthmatic drugs were no longer necessary, and none was required during the remainder of his hospital stay. This patient is now being given 50 mgm. ACTH in two divided doses, two days out of each week, to see the effect of this procedure on the duration of freedom from asthma.

The fourth patient had a higher than average initial dosage, 140 mgm. per day (because of error in assay) in his first course which lasted ten days. The second course consisted of five days with 50 mgm. ACTH given each day and was begun 15 days after mild recurrence in which adjuvant therapy was required only at night. Remission from this second course lasted slightly longer than after the first.

In patient #5, both first and second courses were given with the same initial dose, duration of course one being twelve days as opposed to five days for the second. Remission in the second instance was but 11 days as compared with 86 for the first, although the asthma was much less severe.

In the sixth and seventh patients, the first and second courses were very similar and the duration of remissions, brief in both, was almost identical after the two courses.

In summary of the effects of subsequent courses of ACTH given 6 to 224 days after asthmatic relapse had occurred, it may be said that beneficial response was in every instance just as prompt and just as complete as with the first course. When the same starting dose was used but the length of administration and total dose decreased, the duration of the remission induced was greatly shortened in three (cases 2, 3 and 5); on the other hand, patient #4 achieved an equally long remission from one-third the initial dose and one-third the total dose. In one patient doubling the initial dose (25 up to 50 mgm. per day) resulted in a faster remission and a ten-fold increase in the duration of freedom from asthma, despite the fact that his total dosage in the two courses was the same. It should perhaps be re-emphasized that in no instance had the severity of the asthma reached the same degree as it was before the initial course of ACTH was given.

Treatment with Cortisone

Cortisone has been given to five patients with asthma. With one exception their asthma was similar in type and severity to that of the group who received ACTH. To patients 1, 2, 3 and 4 (first course) the dose of cortisone given was 200 mgm. on the first day and 100 mgm. thereafter for seven days (Table 3). A second course with double this dosage was given to patient #4, 45 days after the first course at a time when the asthma was of approximately equal severity. To the fifth

patient cortisone was given 300 mgm. the first two days, and 200 mgm. thereafter for nine days. The daily dose was divided into four equal parts and administered intramuscularly at intervals of six hours.

The only patient in this group to achieve complete subjective and objective freedom from asthma was patient #5, who not only received the largest doses of cortisone, but whose asthma was very mild as compared with any other member of this series. The medication was given to him primarily to note its effect on a large accumulation of nasal polypi. His remission from asthma lasted 51 days, the symptoms recurring with approximately their former severity coincident with an

TABLE 3

Dosage of Cortisone Given to Four Patients and to One Patient Twice and Resulting Remission and Effect on Eosinophile Count

CASE	HISTORY NO.	SEX	AGE	ASTHMA		CORTISONE			EOSINOPHILES				REMISSION	
				Yrs.	Type	Total	Initial dose	Days	Before RX	Lower after RX	% fall	Day	%	Day
						mg.	*mg.*							
1 H. S.	230494	M	63	27	I	900	200	8	440	319	27	9	40	7
2 H. P.	523671	M	50	20	E & I	900	200	8	1221	77	94	6	25	7
3 F. L.	434666	F	54	27	I	900	200	8	1342	22	98	8	50	8
4 S. S.	118083	F	57	7	I	900	200	8	605	66	89	2	30	6
						1800	400	8	1892	11	99	9	25	6
5 J. S.	530174	M	40	4	E & I	2300	300	11	231	66	72	6	100	5

upper respiratory infection. The other patients failed to improve more than moderately in their own opinion or as judged by the various criteria described above. None of these patients showed further improvement after cortisone was stopped.

Four of the patients treated originally with cortisone were later given ACTH (Table 4). Patients 1, 2 and 4 received ACTH eight days after completion of their courses of cortisone. The dose of ACTH was larger than usual, due to an error in assay, yet in two of the three symptoms were no more improved than they had been with cortisone. It was felt that perhaps the capacity of the adrenal to respond to ACTH had been impeded by the previous cortisone, yet the eosinophil response, edema formation and rise in urinary 17-ketosteroids (of the two whose urine

was studied) revealed as vigorous response to ACTH as in the other patients to whom ACTH was given. In addition, patient #3 received a third course of ACTH after an interval of five months. The initial dose on this occasion was 75 mgm. as compared to 140 with the first course of ACTH and the total amount 785 mgm. over thirteen days as compared to 798 mgm. over ten days. With the third course there was complete suppression of the asthma. Patient #2 achieved a complete remission when ACTH was given eight days after completion of the cortisone course.

TABLE 4

Results of ACTH Given 8 Days after a Previous Course of Cortisone, and After Further Intervals Following the Cortisone

CASE	HISTORY NO.	ACTH				DAYS SINCE CORTISONE	REMISSION			EOSINOPHILES			
		COURSE	Total	Initial dose/day	Days		%	Day	Duration	Max.	Min.	% fall	On day
			mg.	mg.									
1 H. P.	523671	1	798	140	10	8	50	7	—	440	11	97	5
2 S. S.	118083	1	798	140	10	8	100	8	14	187	0	100	2
		2	650	50	13	54	100	13	14	671	0	100	13
3 H. S.	230494	1	798	140	10	8	50	6	—	418	0	100	3
		2	1150	50	22	75	100	21	?	484	0	100	3
4 F. L.	434666	2	570	100	10	60	80	10	—	1034	0	100	10

A comparison of the results in this small group treated with cortisone with the results of the larger group treated with ACTH indicates that, in the dosages of the two drugs employed, cortisone compares unfavorably with ACTH in alleviating the signs and symptoms of bronchial asthma. Clinical improvement was, furthermore, noted earlier in every instance after ACTH than after cortisone. From the small number of observations it cannot be decided whether a previous course of cortisone, ending eight days before ACTH was used, reduced the likelihood of optimal clinical response to ACTH.

Results of the control studies

The procedure outlined was carried out in eleven instances, using ACTH with seven patients, cortisone with four. In the group receiving

ACTH (Table 5), four of the seven received placebo first, and during the five or eight days there was no evidence of clinical improvement. By the fifth day of ACTH administration, there was uniform agreement of improvement in all; in four, all symptoms and signs of asthma had disappeared, in the remaining three improvement was estimated to be better than 75 per cent.

Results in the four patients in the cortisone group were more difficult to evaluate, since none of these patients achieved more than 50 per cent amelioration of their symptoms even at the end of cortisone

TABLE 5

Results in Control Series Treated with ACTH and Placebos

CASE	PLACEBO FIRST	PLACEBO AFTER ACTH	CLINICAL EVALUATION AT DAY 5	CLINICAL EVALUATION AT DAY 15
1 B. M.	X		No change	Complete remission
2 J. B.		X	Complete remission	Complete remission
3 D. H.		X	Complete remission	Complete remission
4 M. H.	X		No change	Complete remission
5 H. N.	X		No change	Complete remission
6 J. F.		X	80% improvement	Complete remission
7 F. L.	X		No change	80% improvement

For details see text.

administration. However, at the fifth day there was a uniformity of opinion that no improvement was present in the two patients who had received placebo, whereas slight or doubtful improvement was the interpretation after five days of cortisone.

Clinical evaluation at the 15th day disclosed that six of the seven patients in the ACTH group were entirely free of asthma; the seventh was adjudged 80 per cent improved. In the group receiving cortisone, it was judged at the 15th day that the patients were all better, but the improvement was variously estimated between 25 and 50 per cent. It was obvious in the group treated with ACTH that the results were clear cut in their indication that the clinical improvement following ACTH is due to the effects of the hormone and cannot be attributed to environmental or psychogenic factors.

COLLATERAL STUDIES

Eosinophils

Eosinophil counts were obtained on all the patients four hours after the first medication and each morning thereafter until the lowest level was reached. In the patients given ACTH (Tables 1 and 2), maximum fall in eosinophils occurred between the second and seventh days with one exception (second course of patient 6 in Table 2). In those patients who achieved complete remissions from their asthma, the fall in eosinophils was 72 per cent or greater, with the single exception of patient 13, who despite entire freedom from asthma within five days never manifested reduction in eosinophils to more than 50 per cent of his starting level. In the four patients whose asthma was not completely relieved, there was an equally great and prompt fall in eosinophils in three (patients 16, 18 and 19 in Table 1), though only a 23 per cent fall in patient 17. Reduction in the blood eosinophil count has been considered the most sensitive test of adrenal cortical activity (2). From this experience with asthmatic patients one might conclude that maximal relief from asthma may not occur unless the eosinophil count falls 75 per cent by the fifth day of administration, but a 90 per cent or better fall in eosinophils need not indicate that good clinical response will occur. In those patients treated with cortisone or with cortisone and ACTH at different times (Tables 3 and 4), the eosinophil fall with ACTH is seen to be usually more prompt. Some patients showed 100 per cent reduction of eosinophils during cortisone therapy without complete alleviation of asthma.

Throughout the entire group of patients who achieved complete remissions under ACTH, there is a striking correlation between the day on which freedom from asthma became total and the day on which maximum eosinophil fall was reached. Exceptions were always on the side of maximal eosinophil fall preceding complete symptomatic remission, as exemplified by patients 10 and 11 in Table 1.

Toward the end of each course of ACTH, usually when the dose fell below 30 mgm. per day, the eosinophil count rose (though rarely to the initial height), while the asthma remained completely in abeyance. Thus, the rise in eosinophils, after previous fall under the influence of ACTH, offered no clue as to the duration of the remission or the in-

cipiency of symptomatic relapse. Chart I depicts a typical pattern of the eosinophil count in relation to asthmatic symptoms during and after administration of ACTH.

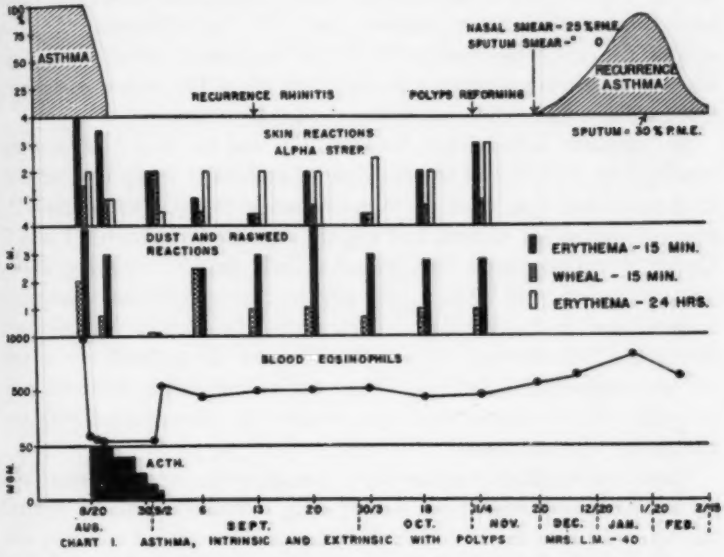

CHART I. THE RESPONSE TO ACTH OF SYMPTOMS AND THE BLOOD EOSINOPHILES IN A PATIENT WITH ASTHMA.

Skin reactions to various antigens

Skin tests to several inhalent and bacterial antigens were made prior to, during and after ACTH and cortisone administration. The majority of the tests carried out during drug administration were done on or between the third to the fifth day of therapy. Injections were made intradermally on the forearm or upper arm using a 25 gauge needle. As a rule, skin tests were carried out only once during drug administration for fear that repeated injections of antigens might modify not only the local skin response but also the antibody titer. In three patients giving typical skin reactions to ragweed pollen, the serum reagin titer using the serum dilution method, was determined. One recipient only was used for the several sera obtained from each individual patient.

In the majority of patients the immediate skin reactions to pollens, dust and to bacterial antigens, and also the 24-hour reactions to the latter were partially or completely suppressed. In several patients, after ACTH administration was stopped the skin reactions were larger and more intense than those observed prior to drug administration. In several the erythema observed during the treatment period, though as large in extent as noted prior to injections of ACTH, was less intense, and the immediate whealing response was also reduced.

No constant relationship between the size of skin reactions as modified by ACTH and the response of asthmatic symptoms to this drug was noted. Skin reactions were reduced on the third day of ACTH, at a time when the asthma had greatly improved in patients 1 and 7 (Table 1) and symptoms disappeared entirely the following day. However, in patient 1 of Table 4, the skin reactions to inhalant antigens were reduced on the fifth day, but maximal relief from asthma did not obtain until the seventh day of ACTH, and the patient was never entirely relieved of symptoms. There was no correlation between gain in weight which occurred in 50 per cent of the cases studied with the changes in skin reactions.

There was variability in the time of reappearance of skin reactions when suppression was noted during drug administration. In several patients who were tested within three to five days after treatment was terminated, the reactions had reappeared, a few exceeding the pre-treatment size. In others, suppression of the reactions was noted up to two weeks beyond the period of hormone administration. In Case 1, Table 1, the skin reactions as recorded were still suppressed on the second day after ACTH was stopped. When the tests were repeated on the sixth post-treatment day reactions to four antigens had reappeared but the partial suppression of the dust reaction remained about the same.

Five patients in the series gave typical immediate reactions to inhalant antigens, three to ragweed pollens and two to dust. Two of the former were clinically sensitive to ragweed pollen and asthmatic symptoms were worse during the ragweed season. Significant reduction in skin reactions was noted in four of the five patients while receiving ACTH, and essentially no change was observed in the fifth.

The serum reagin titer determined in the three pollen sensitive cases,

TABLE 6
Intrinsic Asthma

	DEC. 10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Staph. Aureus	1.0 0	1.0	+ −				+ −	0.5				0								0.6 1.2	1.0
Pneumococcus	1.0 2.5	2.5	+ −				+ −	0.5				0								0.5 1.0	1.0
H. Influenzae	1.0 3.75	2.5	+ −				+ −	1.0				0								0.8 2.0	+ −
Staph. Toxin	1.0 2.5	3.0	2.5				0.7 2.5	1.5				0.9 2.5	2.0 *							0.9 2.5	3.5
Tuberculin 1–100,000	0	0.5	0.5				0	0.7				0	0	0						0	2.0
Tuberculin 1–10,000	0	1.75	1.75				0	1.0				0	0.05 ±	0						0	1.5
Dust	1.0 2.5	−	−				+ −					0								+ −	−
Eosinophiles	286		300	99	55	55				33		44		264					429		
Weight	136½		136	134½	135	136½	138¾	138	140	141	141½	142½	143	140½	140½	139½	137	136½	136½	136½	137¾
ACTH mgm.				140	140	105	105	70	70	56	56	28	28	0	0	0	0	0	0	0	0

Effect of ACTH (Case 7, Table 1), on skin reactions to bacterial and inhalant antigens (dust). First column of figures of each series of tests represent immediate reactions; second column, the 24-hour reactions; and third column the 48-hour reactions. With one exception, definite reduction in all reactions on the 4th day of ACTH, and complete suppression on 9th day. When retested on 7th post-treatment day, reactions reappeared.

Upper numerals ÷ diameter of wheals.

Lower numerals ÷ diameter of erythema.

Where only one row of figures is recorded, values represent diameter of erythema.

* Mild reaction, erythema very faint.

I very faint reaction, erythema only.

in two of which the skin reactions were suppressed (Patient 1, Table 1, Patient 1, Table 4), was not significantly altered. In Patient 1 of Table 1 passive transfer studies were done on the third and fifth days of drugs administration, and on the sixth day after withdrawal of ACTH. It is fully realized that these observations on skin reaction to inhalant antigens and serum reagin titers are very limited and that no definite conclusions can be drawn.

Immediate and delayed (24 hour) reactions to bacterial antigens were significantly reduced during ACTH administration. The antigens used were bacterial vaccines prepared in the usual manner and included strains of Staphylococcus albus and aureus, several strains of streptococci, one Pneumococcus, Staphylococcus Toxin, and Tuberculin (Old Tuberculin). Positive immediate wheal-erythema reactions were obtained in ten patients, and in seven the reactions were significantly reduced during ACTH administration. The 24-hour reactions were reduced in eight of eleven patients. *Table* 6 (Case 7, Table 1) illustrates a typical experiment in this group, and includes the reactions to Tuberculin which were likewise suppressed. Of the three patients exhibiting positive Tuberculin reactions prior to ACTH, significant suppression of the reaction was noted in all three instances.

The comparative effect of cortisone and ACTH administration on skin reactions to both inhalant and bacterial antigens was observed in four patients. Cortisone preceded ACTH administration in each case. In the dosage used cortisone was definitely less effective than ACTH in reducing skin reactions. In two patients (No. 1, 4, Table 4) exhibiting positive reactions to pollens and/or dust, the reactions were definitely reduced in one, and slightly in the other. When ACTH was given further reduction in size of the reactions was noted.

Of the immediate and delayed (24 hour) bacterial reactions obtained in the four patients prior to cortisone, the only change was in the delayed reactions (24 hour) in one patient. However, when ACTH was administered, marked reduction of both immediate and delayed reactions were observed in three, but no further reduction in size of the delayed reactions already suppressed by cortisone was noted.

Metabolic effects

The metabolic effects of ACTH and cortisone in the asthmatic patients followed in general those reported for the entire group of

disease states so far treated in this clinic (3). Weight gain of more than five pounds occurred in approximately two-thirds of the patients; manifest edema developed in one-half. There was prompt return to pretreatment status within a few days of discontinuation of the drugs; often in the patients given ACTH weight loss began when the dose was reduced below 30 mgm. per day. Rises in blood pressure of more than 25 mm. systolic or 15 mm. diastolic occurred in five of the twenty-three patients. Fasting blood sugar rose more than 20 mgm. per 100 cc. in 50 per cent, but in no instance did glycosuria occur. No patient developed hirsutism, amenorrhea or striae. Acne appeared in six of the group and was quite severe in one. One patient developed asymptomatic hypokalemia; she was elderly and the most undernourished in the group. Serum CO_2 rose between 3 and 8 meq. in 50 per cent of the group. The hematocrit fell in all patients, the average being 7 mm. (Wintrobe); the degree of blood dilution manifested by the hematocrit was, however, not correlated with the amount of weight gain or the presence or absence of edema.

DISCUSSION

It has been conclusively demonstrated that stimulation of the adrenal glands by ACTH and administration of cortisone result in alleviation of the clinical manifestations of chronic bronchial asthma in the majority of cases treated. Coincidentally with the studies outlined in this report, Randolph and Rollins (4) and Rose (5) observed improvement in asthmatic patients following exhibition of ACTH. The site of operation and mechanism of the beneficial actions are as yet unknown.

The various factors which determine the length of freedom from symptoms have not been elucidated, but it is quite clear that an equally satisfactory response can be obtained following a second and third course of treatment without the necessity for more intense or prolonged administration. The experiences of the past year which are reported here indicate, when one reviews the duration of the remissions obtained, that this form of therapy represents an important advance in the management of patients with severe asthma who cannot be satisfactorily controlled by the other means available. In one instance of severe status asthmaticus described the administration of ACTH was a life-saving measure. Much more is to be learned concerning the ideal

form of treatment with ACTH and cortisone and this may prove variable from patient to patient. The evidence thus far suggests that there may be a reasonably predictable period of remission for each patient of such duration that intermittent short courses of ACTH can keep the intractable type of asthma under continual control. However, there is little known at present about the effects of long-term administration of ACTH and further experience is needed before the value and safety of this type of therapy can be fully assessed.

Adrenal cortical extracts have previously been given to patients with bronchial asthma. Fineman (6) administered small doses of eschatin at one to three day intervals because the weakness, anorexia, weight loss, low blood pressure and hypochlorhydria, frequently seen in sufferers from chronic asthma, suggested the presence of adrenal insufficiency. Two of the four patients so treated showed improvement. Cohen and Rudolph (7) used Interrenalin (Rogoff), but their patients manifested no evidence of any change in the severity of the asthma.

Evidence that the adrenal glands are in some way related to the phenomena of hypersensitivity is not new. Dale suggested that histamine released from the tissues might be the causative agent in anaphylactic shock. Though many discrepancies have fallen in the way of this theory, there is still a certain body of evidence indicating that histamine or a related substance is one of the factors in the anaphylactic type of allergy. Dale (8) found that the blood pressure lowering effect of histamine is ten-fold greater in the adrenalectomized than in normal cats and Banting and Gairns (9) observed histamine to be thirty times more toxic in dogs whose adrenal glands had been removed. Kellaway and Cowell (10) showed that it was loss of the adrenal cortex rather than the medulla which was responsible for the increased toxicity of histamine. In all of the cases of asthma studied by Rose there was an increased excretion of histamine in the urine before treatment and in five patients marked reduction in output of histamine after ACTH therapy was begun. Preliminary observations on certain of our patients by Dr. David B. Grob has shown similar results, but in many instances as the dose of ACTH was reduced excretion of histamine again rose at times exceeding the pretreatment amounts. Grob also administered histamine intracutaneously both before treatment and when the asthma was in remission under ACTH therapy. At each time the cutaneous

response was identical. Furthermore, curare injected intracutaneously (11) produced the same response whether ACTH was being administered or not. Thus, ACTH in doses sufficient to induce a clinical remission in asthmatic patients does not inhibit the capacity of the epidermal tissues to release histamine or respond to its intracutaneous injection. Curry and his coworkers (12) have studied the effect of ACTH on the evanescent attack of asthma induced by the injection of histamine in which there is a reduction in vital capacity and maximum minute ventillation. Significant protection against the action of histamine could not be obtained by the administration of ACTH suggesting that benefit obtained in patients with asthma with the hormone is not through an antihistaminic action.

Asthma is a disease generally recognized as resulting from sensitivity to an antigen-antibody combination. Mirick (13) has shown that, in patients in whom either ACTH or cortisone is being administered, antibodies to pneumococcus polysaccharide are produced quantitatively and qualitatively just as well as in normal controls. Chow finds that the titer of complement in the plasma rises when ACTH is administered; in contrast to the inactivation of complement by nitrogen mustard (14), which also suppresses local tissue sensitivity (15). In the few patients in this series which were studied serum reagin titers did not change during ACTH therapy. There is no evidence thus far that the beneficial action of ACTH in asthma is mediated by a reduction of either circulating antibody or complement.

The impression is gained that the "resistance" to the hypersensitivity which is conferred by the adrenal activation is a relative one, capable of being broken through if the challenging stimulus is large enough. The degree and duration of the resistance to the asthma seems highly variable, and dependent on factors as yet undetermined. Thus far, however, no patients have been met in whom there has not been conferred considerable clinical benefit from exhibition of ACTH.

A much larger experience with the use of ACTH and cortisone in asthmatic subjects, together with a greater knowledge of their mode of action, is required before a proper evaluation of the therapeutic implications of these agents can be made. On the present evidence it seems that they may be used profitably as therapeutic adjuvants for brief periods in severe asthmatic states, provided they are not given

to patients to whom the other physiologic effects of these hormones might prove dangerous.

SUMMARY

1. It has been conclusively demonstrated that stimulation of the adrenal glands by ACTH and administration of cortisone in sufficient doses have a beneficial effect on the clinical manifestations of chronic bronchial asthma. Complete remissions lasting from four days to over ten months have been obtained.

2. The various factors which determine the length of freedom from symptoms have not been determined, but an equally satisfactory response can be obtained following a second and third course of treatment with ACTH.

3. A much longer experience is necessary before a proper evaluation of the therapeutic implications of these agents can be made. At present it seems that they may be used profitably for brief periods of time in severe asthmatic states, provided they are not given to patients to whom other physiological effects of these hormones might prove dangerous.

ACKNOWLEDGEMENTS

Part of the ACTH used in these studies was supplied by Armour and Company through the courtesy of Dr. John R. Mote. The cortisone and part of the ACTH was purchased through a grant-in-aid from the U. S. Public Health Service. The metabolic studies, to be reported later in detail, were supported in part by a contract between the Johns Hopkins University and the Office of Naval Research.

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APPENDIX

Three case reports will be given, representative of the entire group and showing some special feature of interest for discussion.

Case 1

M. G. (JHH 528824).

A 52-year-old white male butcher, who had no family history of allergic disease. In 1941, during treatment for a parotid abscess with a sulfonamide, hives appeared and the drug was stopped. In July, 1947 he suddenly developed bouts of sneezing and rhinorrhea. Nasal polypi were removed without alteration of the symptoms which continued summer and winter but were readily relieved by antihistaminic drugs.

On September 22, 1949 the patient wakened feeling weak and dyspneic. His doctor made the diagnosis of asthma and gave aminophyllin both intramuscularly and intravenously. Respiration became progressively more difficult and the following day the patient was admitted to a hospital where, for two weeks, he was treated in an oxygen tent with various antiasthmatic drugs. Improvement was only transitory, and in the succeeding four months he was hospitalized on five occasions. In two especially grave episodes, the patient became unconscious and developed circulatory collapse. At no time since onset of the asthma, even in

hospitals and with the use of every adjuvant measure, had he even temporarily experienced comfortable breathing.

He was admitted on February 13, 1950, having lost approximately 30 lbs. in weight since the onset of his illness. Height was 64 inches, weight 129 lbs. Temperature normal, pulse 100, respirations 28, blood pressure 150/90. Oral hygiene was poor. He was in obvious distress, using the accessory muscles of respiration. Nail beds and lips were cyanotic. There was stridor, and asthmatic wheezes were audible all over the lungs. The chest was emphysematous. No abnormalities were made out in examination of the heart, abdomen, genitalia or nervous system. Urine was normal as was the erythron. Eosinophiles were 15 to 30% of the total white count which varied between 8 and 13 thousand. Serologic tests for syphilis were negative. Roentgenogram of the chest revealed only emphysema and old pleural adhesions at the right base. The laryngologist found small polyps in the ethmoid regions, and there appeared to be polyps or cysts in the antra radiologically. Vital capacity was 1.8 litres, after epinephrine 2.4 litres. Electrocardiogram was interpreted as showing left axis deviation and minor non-specific S-T changes. Serum CO_2 was 30 and chloride 97 meq. per litre; blood non-protein nitrogen and sugar were normal.

The patient's condition changed but little in the following month, during which time he was never free of respiratory distress. Sputum consisted of 1 to 2 ounces of thick whitish material, culture of which grew no pathogens. One or more times daily his steady asthmatic state would become suddenly worse, and for these exacerbations intravenous aminophyllin gave the best, but only partial, relief. He was given at varying times oxygen, helium, subcutaneous epinephrine in aqueous solution and in oil, aminophyllin, rectal ether, epinephrine spray, Isoprel, iodides and penicillin. His attending physicians, having exhausted their therapeutic armamentarium, suggested that ACTH be tried. At this time the physical and laboratory examinations were essentially as recorded above. A muscle biopsy disclosed no evidence of periarteritis nodosa.

ACTH was begun at noon on March 9th. 50 mg. was given as the initial dose and thereafter 25 mg. was given every six hours for 48 hours. From the 11th to the 13th he received 80 mg. ACTH per day; from the 13th to the 15th of March 50 mg. per day; from the 15th to the 17th 40 mg. per day, and 20 mg. per day until the 19th when the drug was discontinued.

On the afternoon of March 10th, 24 hours after ACTH was begun, improvement became apparent. During the previous 24 hours, the patient had constant severe respiratory difficulty, despite sitting bolt upright, and despite administration of helium and oxygen, together with the following drugs: 2 cc. epinephrine aqueous, 3 cc. epinephrine in oil, 2.5 gms. aminophyllin intravenously and 45 cc. paraldehyde. He had been unable to take any food and was fed parenterally. By supper time on the 10th he was able to eat and at 8 p.m. was reading a newspaper. Oxygen and helium were not necessary thereafter. On the 11th of March he was able to walk about and perform his own toilet with little discomfort. Both objectively and subjectively he improved steadily, and from the 11th to the 13th required but three

injections of epinephrine and no further adjuvant medication was given. He had lost all subjective asthma by March 16th, but the chest was not clear to stethoscopic examination until March 25th. On the 28th the patient was discharged entirely comfortable, though on this day the examiner heard again a few transient wheezes after coughing.

Other features of interest during his course include the following: When ACTH was started, the eosinophile count was 1496 per c.mm.; eight hours later it was 242; the following morning 55 and 30 hours after beginning the drug, the count was zero. Thereafter the daily count fluctuated between 100 and zero (average 30) until March 20th when there was a sudden rise to 700 eosinophiles per c.mm. This was the morning after ACTH had been discontinued, and sterile saline injections were being given. From this time until discharge, the eosinophile count ranged between 300 and 500 per c.m ı.

The blood pressure *fell* progressively during ACTH administration, coincident with improvement in the asthmatic status, and likewise coincident with reduction in the enormous quantity of drugs he had been receiving, including epinephrine. By the third day the patient was eating well and soon developed a ravenous appetite. There was a 4 lb. gain in weight over the first three days of ACTH; thereafter the weight remained essentially stationary until discharge. His diet, while on ACTH, was as desired except that there was restriction of sodium chloride to 4 grams daily.

Serum CO_2 began at 30 meq. per litre and chloride at 96.8. After one week of ACTH, CO_2 was 34.3, chloride 100 and the serum sodium had risen from 136.8 to 146 mg/e. At this time serum potassium was 3 meq.

Four days after ACTH was discontinued, when the patient was continuing to gratify a very large appetite, he experienced postprandially one evening substernal discomfort lasting for half an hour. The symptoms disappeared spontaneously and did not recur; there were no cardiovascular changes noted and the electrocardiogram showed no alteration.

After discharge the patient remained free of asthma for more than two months. At the end of three months he is still active and suffers only minor asthmatic discomfort easily relieved by sprays.

Case 2

M. S. (JHH 435221).

A 26-year-old white married female had for seven years suffered with repeated upper respiratory infections. A maternal aunt has asthma. Wheezing respiration began three years ago during a cold; the first severe attack of asthma occurred two years ago during an attack of bronchitis. It was known that she had a chronic infection of the right lower lobe, thought to be bronchiectasis or congenital cystic disease. She did not react to inhalants by skin tests. Acute febrile respiratory episodes responded to penicillin, but the patient was never free of a productive cough

or asthmatic wheezing and was incapacitated so that she had to be waited upon at home.

The patient was admitted on March 8, 1950 with an exacerbation of her asthma. She was emaciated (weight 85 lbs.), anxious, moderately cyanotic, severely orthopneic. There were wheezes and sticky rales throughout both lungs. There were no signs of cardiac insufficiency; blood pressure was normal; abdominal, pelvic and neurologic examinations revealed no abnormalities. There was no fever, and the recovered sputum was small in amount, though it was believed that she swallowed large quantities. Cultures of the sputum disclosed normal flora, and no tubercle bacilli were found. Routine studies of the blood revealed 6 to 8% eosinophiles; urine and stool examinations were normal.

Penicillin and aureomycin brought about little improvement in the patient's symptoms which were mainly those of constant asthma with episodes of severe exacerbation in which she became cyanotic and often vomited. Oxygen, epinephrine, aminophyllin and antihistaminic drugs gave only transient and partial relief. Bronchoscopy and pulmonary visualization with lipiodol could not be carried out satisfactorily. For more than a month, every effort was made to cope with asthma in order to evaluate the pulmonary infection and prepare her for possible surgical therapy. These measures were unavailing, and the patient's status was unimproved six weeks after her admission.

It was decided to use ACTH therapeutically in order to overcome the asthma, and make bronchoscopic and lipiodol studies possible. At noon on April 25th, ACTH was begun, 80 mg. Armour standard being given daily until May 2nd, 50 mg. per day until May 5th, 37.5 mg. per day to May 7th and 25 mg. per day until discontinuance on May 9th.

Within 12 hours the patient felt more comfortable, and she required but one injection of epinephrine during the night. By the next morning, breathing was easier than at any time since admission and the patient ate breakfast without difficulty and was laughing and talking. The patient continued to improve steadily and by May 2nd there were neither subjective nor objective evidences of asthma. Sputum virtually disappeared, and the patient was able to be up and about the ward freely. Appetite was excellent.

On May 4th bronchoscopy and bronchography were carried out successfully with little discomfort to the patient. Bronchograms of the other lung were made on May 9th with no difficulty. Since these studies revealed saccular bronchiectasis of the right middle lobe and the other lobes were not involved, on May 17th right middle lobectomy was carried out. Sections revealed saccular bronchiectasis and areas of partial atelectasis. Postoperative course was uneventful, and there has been no recurrence of asthma to this date (two months).

Collateral studies carried out coincident with ACTH administration disclosed the following: Eosinophiles, prior to ACTH, varied between 5 and 600 per c.mm., fell to 250 eighteen hours after the first dose, to 130 at 42 hours, but never below this point. The counts ranged between 165 and 275 until May 9th, one day after

ACTH was discontinued, when they rose to 935 and remained in this area thereafter. The eosinophiles fell to zero during the first 48 hours after operation.

On a routine ward diet, the patient gained 4 lbs. in the first four treatment days; weight was stable thereafter until operation. No edema was apparent. Hematocrit fell from 41 mm. (Wintrobe) to 34 mm. on May 5th, but had returned to 40 mm. by May 15th. There was no significant change in blood pressure, or in the concentration of chloride, CO_2 or total protein in the serum.

Case 3

R. M. (JHH 511025).

A registered nurse, aged 40, who first entered the hospital in November, 1932 with a febrile pneumonitis. For two months she remained ill with fever, cough, dyspnea and extensive infiltrative lesions of the lungs. White blood count ranged between 10 and 15 thousand per c.mm. with eosinophils always between 20 and 30 per cent. No tubercle bacilli or other pathogens were ever recovered from the sputum. Recovery set in spontaneously and was amazingly rapid with considerable clearing of the roentgenogram. She was sent to a tuberculosis sanitorium in March 1933 for bed rest. In April 1933, at the sanitorium, the former symptoms recurred and for six weeks she again suffered from a severe febrile respiratory illness. Roentgenograms again revealed extensive infiltration in both lung fields extending out from the hilar areas. Again there was complete recovery.

During the winter of 1933–1934 she developed constant nasal congestion which has persisted. The sense of taste and smell gradually disappeared.

In 1946, during a short febrile illness thought to be bronchitis, wheezing first appeared. During the next three years asthmatic symptoms steadily increased, the nose remained constantly obstructed and nasal polypi began to develop.

In May, 1949 all symptoms became worse. Dyspnea prevented walking except at the slowest pace, and orthopnea was so severe as to require the upright position for sleep. Pyribenzamine relieved the nasal symptoms slightly but did not alleviate the asthma. For two weeks prior to admission to the hospital on August 17, 1949 asthma had been constant and severe with no relief from sedatives, antihistamines and sympathomimetic drugs.

Examination revealed oral temperature of 99.4 F., pulse 128, respirations 36, B.P. 124/76. She appeared tired and ill with noisy labored breathing. The chest was emphysematous. Percussion note was hyperresonant and sibilant and sonorous rales were everywhere audible over the lungs. The nose was completely obstructed by large nasal polypi readily visible. Cardiac, abdominal and neurological examination revealed no abnormalities.

Serologic tests for syphilis negative. Hemoglobin 16 gms., hematocrit 49, sedimentation rate 0. White blood count 8 thousand, eosinophils 8.5 %. The urine and stool were normal as were the blood sugar and NPN. Roentgenogram disclosed fibroid infiltration of the right apex without evidence of activity, thickened pleura at both apices, normal heart and aorta.

During the first three hospital days the patient experienced constant respiratory difficulty despite all the simpler antiasthmatic remedies. Each night rectal ether was required to afford rest. Coughing was very frequent and severe when awake, productive of about a cupful of mucoid sputum per day; normal flora were grown on culture.

It had been planned to remove the nasal polypi and perform radical antral operations when the asthmatic state had been sufficiently controlled. Since no improvement had been manifest within the three days of hospitalization it was decided to see the possible effect of ACTH administration. This was begun at 6 a.m. August 20 in doses of 12.5 mgm. (Armour Standard) given every 6 hours. The clinical course is graphically represented in Chart I.

Within three hours after the first injection the patient became aware of extraordinary subjective relief. At five hours respirations had fallen to 20 per minute, pulse rate was 92, and only a few inspiratory and expiratory wheezes were heard on auscultation. By midafternoon the patient could inspire fully, which she rarely had been able to do for three years. That night she slept without sedation and the following day she performed her own toilet, walked in the corridor without respiratory embarrassment and could lie flat on the bed. No adjuvant therapy was required after ACTH was begun. On the third day of ACTH the patient suddenly noticed that she could taste and smell. It was discovered that the nasal polypi had shrunk and breathing space was plentiful. One of the earliest evidences of improvement noted by this patient had been diminution in both the nasal and bronchial secretions which had practically disappeared after 48 hours on ACTH. On the fourth day of administration of the hormone all signs and symptoms of asthma had disappeared. Asthmatic symptoms did not recur for 86 days after discharge from the hospital. Total ACTH given was 440 mgm. over a period of 12 days.

224 days after ending of the first course of ACTH the patient returned to the hospital for a second course of the drug. At this time the asthma was not nearly so severe as when the first course was given. 40 mgm. ACTH was administered per day for five days. Improvement was again manifest within 4 hours of the first dose. All signs and symptoms of asthma had disappeared by the fourth day. However, 11 days after ACTH was stopped the patient began to notice wheezing and mild respiratory embarrassment.

OBSERVATIONS ON CHANGES TAKING PLACE IN THE UPPER RESPIRATORY TRACT OF PATIENTS UNDER ACTH AND CORTISONE THERAPY

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When the original study on the effect of ACTH in allergic diseases was planned by Dr. Abner McGehee Harvey and Dr. John Eager Howard, it was decided to have as many cases as possible observed from the point of view of tissue changes in the upper respiratory tract. The techniques available permit direct observation of alterations in the mucous membranes and lymphoid tissue and material for biopsy is easily obtained. These observations were begun in July of 1949, and a preliminary report of the findings was made in October, 1949 (1) at the first conference on ACTH, sponsored by Armour and Company.

Since the beginning of the study, fifty-seven patients have been observed and approximately four hundred examinations have been carried out on this group. Routine study has included palpation of the neck glands, anterior rhinoscopy, examination with the electric nasopharyngoscope, inspection of the mouth, tongue, and throat, and transillumination of the sinuses. X-ray pictures of the sinuses were obtained on admission and at dischage. Nasal polyps were removed from five patients; nasopharyngeal lymphoid tissue was removed from sixteen patients. A total of forty-seven biopsies was performed at varying intervals during the course of treatment.

The fifty-seven cases studied fall into the following groups: Allergies of the respiratory tract, 23; Rheumatoid arthritis, 13; Disseminated lupus erythematosus, 9; Inflammatory diseases of the eye, 3; Periarteritis nodosa, 3; Penicillin reaction, 2; Chronic hepatitis, 1; Pemphigus of the mouth, nose, and eyes, 1*; Myasthenia gravis, 1; Meniere's disease, 1.

* Improvement observed in the specific upper respiratory lesions of pemphigus while under ACTH are to be discussed in a subsequent paper.

The author wishes to express his appreciation of the untiring efforts and unselfish cooperation of Miss Hazel Burke, R.N., Miss Jean Maddy, R.N., and Miss Helen Covington in working many hours to bring this study to a successful conclusion.

No specific pretreatment changes in the nasal mucosa could be correlated with the various diseases under study, except in the group suffering with nasal allergy. Before ACTH or cortisone therapy, the nasal picture seemed to vary with the general condition of the individual, rather than with the type disease from which he suffered. There was a wide range to the appearance of the nasal mucosa. Patients suffering from inflammatory diseases of the eye, the less severe arthritics, the patients with periarteritis nodosa, and two asthmatics, were free from changes in the nose. The mucosa was a healthy pink, there were no unusual discharges, and no evidence of polypoid degeneration was seen around the posterior portions of the turbinates. The large majority of the patients seen presented the picture of pale, moderately swollen mucous membranes in the nose, tending toward slight polypoid changes around the posterior end of the turbinates; this was covered with a mucoid discharge ranging from thick clear to mucopurulent. A few of the very ill patients, especially those suffering from severe lupus erythematosus or very severe rheumatoid arthritis, showed nasal changes characteristic of many debilitating diseases. The membranes of the anterior portion of the nose were swollen, and were either very red or an unhealthy yellowish pink. There were small areas of ulceration especially on the anterior one-third of the septum, and bleeding points were frequently seen in the ulcerated areas. The posterior portion of the turbinates were pale and polypoid. The nostrils contained much crusted or thick mucopurulent discharge which seemed to originate on the surface of the mucous membranes.

GENERAL RESULTS

It was apparent from the beginning of the study that there were certain changes in the upper respiratory passages common to all categories of disease treated with ACTH. Within twelve to seventy-two hours of the institution of adequate doses of ACTH, the nasal mucous membranes of all the patients developed a slate or bluish tinge and became covered with clear thin mucus. Crusting, cloudy or purulent discharges around the turbinates (this does not include those individuals suffering from sinusitis), and ulcerations around the mucous membranes of the anterior nares, rapidly disappeared. The polypoid appearance of the mucous membranes of the posterior ends of the turbinates became

less edematous and changed to a pinkish color, gradually becoming darker by the end of the third or fourth day. These changes were first noticed in most cases within the first twenty-four hours. After the patients had received sufficient ACTH to result in stimulation of the adrenal cortex (eosinophil response, urinary 17-ketosteroid excretion), these changes paralled the clinical improvement in primary disease under treatment in many instances. After therapy had been discontinued, or even in some instances when the dose had been reduced below thirty milligrams a day, the color changes receded in from one to three days, and within another two to three days the discharge from the mucous membranes reappeared.

Those individuals suffereing from nasal obstruction due to swollen, redundant mucous membranes and excessive thick mucoid discharge experienced an improvement in breathing space within four to forty-eight hours after the institution of adequate ACTH therapy.

The third change common to all patients under ACTH therapy was that observed in the lymphoid tissue in the nasopharynx. The tissue became an orange pink and was easily distinguished from the mucous membranes of the surrounding structures. Cloudy or mucopurulent discharges were replaced by a thin layer of clear mucus. The crypts became more prominent and appeared clean. In three cases under observation, it was felt that the lymphoid tissue showed perceptible shrinkage, but this was not noted in the remainder of the patients. The lymphoid tissue changes disappeared within three to four days after the cessation of therapy.

Nine of the fifty-seven cases studied received cortisone therapy. These patients all showed a decrease in nasal secretions. In those individuals suffering from nasal obstruction, there was approximately the same degree of relief following cortisone admininstration as with ACTH therapy. Color change in the mucous membranes was much less marked; in general, it was manifest by a more healthy looking pink color developing in the nasal mucosa about the third or fourth day after the institution of treatment. The bluish color of the nasal mucosa described with ACTH therapy was never observed. No color changes were noted in the lymphoid tissue of the nasopharynx. Discharge around it cleared up somewhat and any inflammation decreased, but there was no noticeable change in the crypts and no change in size.

Results in Patients with Asthma and Nasal Allergy

The most interesting group under study was that suffering from respiratory allergy. Twenty-nine courses of treatment, either ACTH or cortisone, were given to twenty-one individuals. There were nine patients suffering from intrinsic asthma with no significant nasal changes. Eight patients were asthmatic, and also had marked allergic rhinitis with polyp formation. Three patients had asthma and changes of the nasal mucosa denoting allergic rhinitis, but without actual polyp formation. One patient showed allergic rhinitis and marked polyp formation without asthma.

The nine individuals with simple asthma showed the same mucous membrane and lymphoid changes described previously.

The effects on these allergic individuals, showing polyp formation and/or marked polypoid changes in the nasal mucosa, will be described in detail. Three patients with asthma, allergic rhinitis and polyps received alternate courses of ACTH and cortisone more than two months apart. Four patients received two courses of ACTH and one received three.

Under adequate dosage of either ACTH or cortisone, there was uniformly a reduction in size or complete disappearance of nasal polyps. Those patients receiving ACTH showed changes in twenty-four to seventy-two hours. There was first a thickening of the mucous membranes of the polyp, and the translucent appearance changed to a delicate pink. At the same time, the nasal mucosa began to develop a deeper color, polypoid changes regressed, and nasal discharge lessened within twelve to twenty-four hours. As the polyp began to shrink, it gradually assumed the color of the nasal mucosa. (Figure 1). In most individuals, the polyps had just about completely disappeared after two weeks of ACTH therapy. Similar changes developed during cortisone administration, but were, in general, about twenty-four hours slower in appearing, and the color changes in the polyps were less pronounced. One of the three cases receiving both hormones showed less shrinkage of polyps at the end of cortisone therapy than was noted after ACTH.

Nasal polyps reappeared in all but three patients within two weeks to two months after either ACTH or cortisone therapy was stopped. This reappearance seemed to be greatly hastened in the presence of

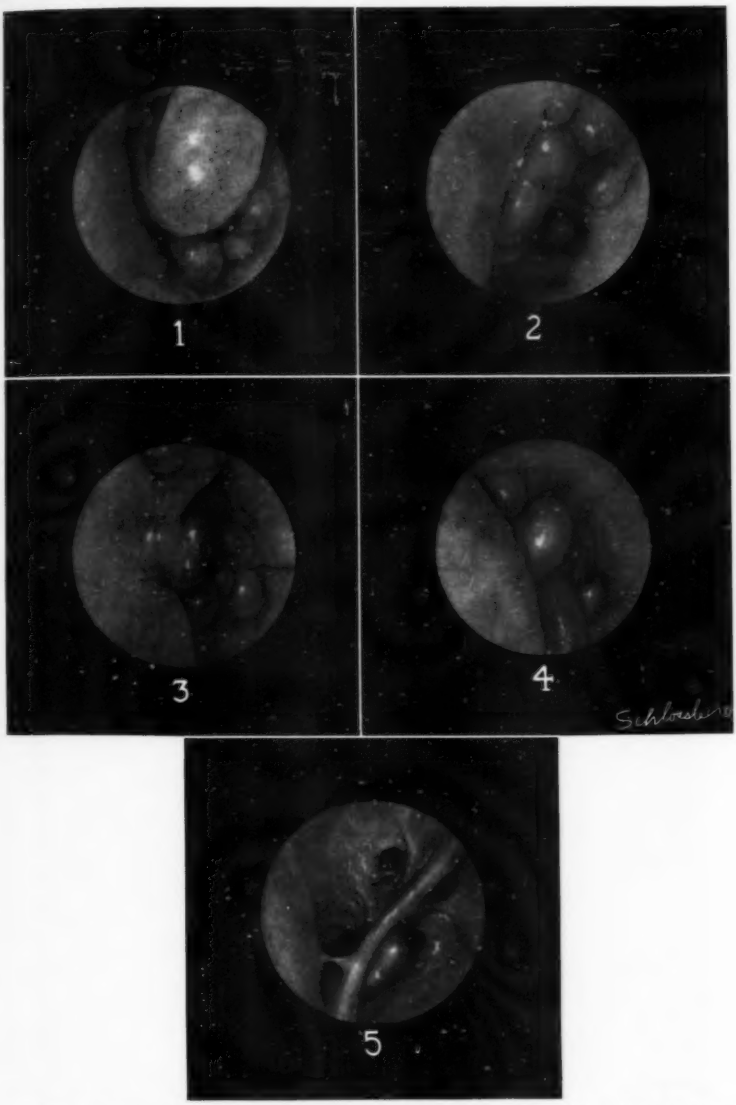

FIG. 1. Observations made through a nasopharyngoscope of the ethmoid sinus area, showing gradual shrinkage of nasal polyps. 1) Before institution of treatment. 2) On third day of ACTH therapy. 3) On the fifth day. 4) On the ninth day. 5) Enlargement of the same area of the ethmoid sinuses showing scar tissue and several ethmoid cells which had been opened at a previous operation. The polyps have disappeared. This drawing was made on the eighteenth day of ACTH therapy.

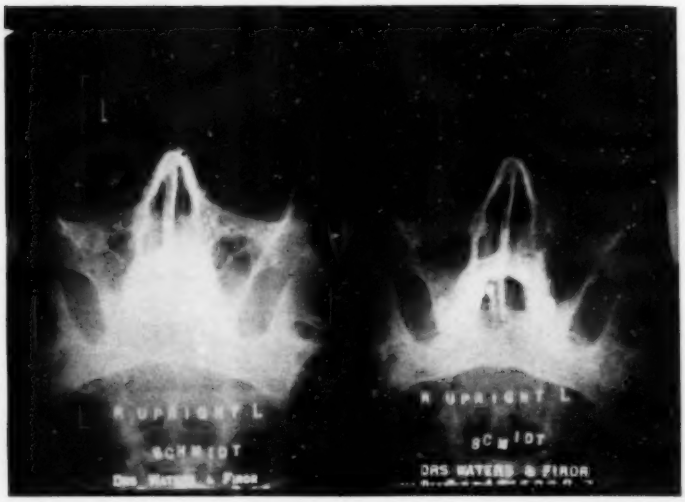

FIG. 2. Comparative x-ray films of the sinuses of a 35 year old male, suffering from allergic rhinitis and bronchial asthma. The first film was taken before administration of ACTH and the second film was taken on the eighth day of treatment.

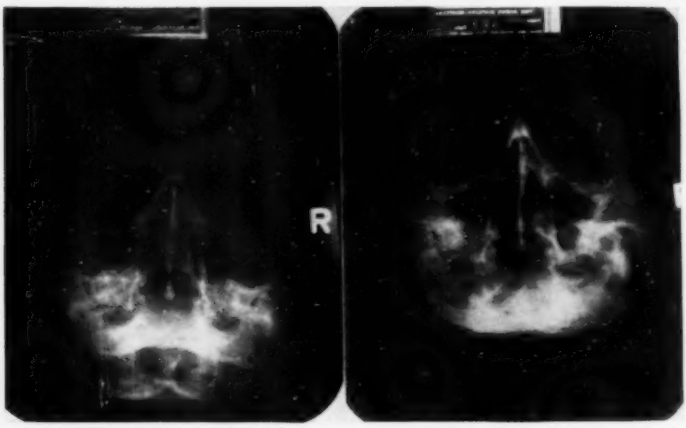

FIG. 3. X-ray films of the sinuses of a 28 year old male before treatment and after eleven days of ACTH therapy. The patient suffered from bronchial asthma and allergic rhinitis. His nose was filled with polyps and the nasal mucosa was much thickened at the time of the first film.

acute upper respiratory infections. The three cases showing no return of nasal polyps had a few very small polyps before therapy was instituted.

Comparative x-ray films, taken before and after treatment, showed much thinning of the lining mucous membranes of the accessory nasal sinuses. Complete disappearance of polyps from the sinuses was noted in a majority of the patients under observation. (Figures 2, 3, 4) The same x-ray changes were evident in those patients under cortisone therapy.

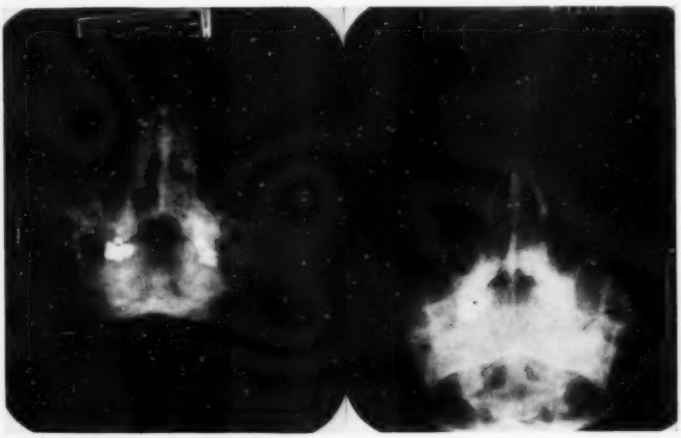

FIG. 4. Sinus films taken before treatment and after eleven days of cortisone therapy. The patient was a male, age 40. He had been suffering from bronchial asthma, allergic rhinitis and nasal polyps. The large polyp seen on the floor of the maxillary sinus in the first film has almost disappeared after the treatment period.

There was a definite correlation between the color changes in the mucous membranes and the development of eosinopenia. However, with the subsequent rise in eosinophils, the mucous membrane changes did not revert to their pretreatment appearance. This correlation between eosinophil count and mucous membrane changes was present in cases under ACTH or cortisone therapy.

LOCAL APPLICATION

One patient suffering from allergic rhinitis and polyp formation without symptoms of asthma was placed on local applications of cortisone.

He had previously been treated with ACTH intramuscularly, and his nasal polyps had disappeared within eighteen days. Five weeks after treatment had been stopped, the polyps began to recur. When he had developed rather marked nasal obstruction, he was given a nasal spray consisting of eight milligrams of cortisone per cubic centimeter. This spray was used three times a day and every seven days he was supplied with a fresh solution. By the end of the first week, the anterior polyps had become pink and had perceptibly shrunk. Within three weeks he had a marked recession in size of the polyps and good breathing space. The nasal discharges were greatly reduced. The posterior polyps showed much slower changes than those in the anterior nares. No color change for more than two weeks in the less accessible polyps would lead one to believe these were local effects and not due to general absorption of the hormone.

MICROSCOPIC CHANGES

Microscopic studies were made on sections of nasopharyngeal lymphoid tissue and nasal polyps. These were carried out under the direction of Dr. Richard Follis of the Department of Pathology. Twenty-six biopsies were performed at various stages of treatment on the nasopharynx of sixteen patients, and twenty-one nasal polyps were removed from five individuals.

The sections of nasopharyngeal lymphoid tissue taken at various intervals after exhibition of ACTH or cortisone demonstrated no significant changes.

The sections of nasal polyps obtained during treatment with both cortisone and ACTH showed a wide variation in the number of eosinophils seen in the polyps. This variation could not be correlated with the dosage level or the clinical course of the treatment. It was felt that these findings were less conclusive, however, than those reached after studying the sections of nasopharyngeal lymphoid tissue.

DISCUSSION

The foregoing report has demonstrated that tissue changes can be shown on direct inspection of the upper air passages in those persons under stimulation by ACTH and cortisone. The changes noted can be correlated with the initial eosinopenia. By such direct observations, it

is possible to determine when a patient has a sufficiently high ACTH level. In several cases it was possible to detect insufficient dosage because the mucous membranes of the nose showed no significant color change, and no decrease could be seen in the nasal discharge. Later reassay of the material used in these cases showed it to be below standard potency.

One reason for undertaking this study was the previous observation of Dougherty and White (2), that increased adrenal cortical function in animals resulted in involution of the normal lymphoid tissues. It was felt that stimulation of such a function in man by the use of ACTH might cause regression of the nasopharyngeal lymphoid tissue. Such results might well have opened a new field of therapy for the otologist. Control of the growth of nasopharyngeal lymphoid tissue around the Eustachian tube would mean control of many middle ear dysfunctions eventually leading to deafness. Such changes did not take place in these experiments, either clinically or microscopically. It is interesting to note that although, clinically, regression was noted in lymph nodes of lymphomatous patients by Pearson, Eliel, and Rawson (3), they were unable to find any microscopic changes in sections of glands biopsied from these patients.

The development of an agent capable of changing, within a few days, the entire picture of nasal allergy opens a fascinating new field of speculation to the otolaryngologist. Using ACTH or cortisone some weeks before operation will make it possible to do necessary sinus surgery without the complication of having the field obscured by nasal polyps. One such case, suffering from severe nasal allergy on a bacterial basis, was seen in our series. Three weeks after the initial ACTH therapy was discontinued his nose filled with polyps. In spite of antibiotic therapy, he continued to show evidence of chronic sinusitis. The polyps by this time had completely obstructed both nostrils. He was given a course of cortisone and his polyps regressed almost completely. Two weeks later a submucous resection of the nasal septum was performed and the ethmoid cells were exenterated. The operation was performed without difficulty and the post-operative course was uneventful. Such surgery might be followed by local cortisone to reduce subsequent polypoid degeneration until post-operative adjustment has taken place.

CONCLUSION

Changes have been noted in the tissues of the upper air passages under adrenal cortical stimulation by ACTH and following the administration of cortisone. During exhibition of ACTH the nasal mucous membranes lose their swelling, develop a slate-pink color and are covered with a thin layer of clear mucus. Polyps lose their translucence, become pink and begin to shrink, in many cases disappearing completely. Such changes seem to be correlated with the initial eosinopenia developing under ACTH therapy. Changes have also been observed in the nasopharyngeal lymphoid tissue. It becomes clearly outlined from its surrounding structures, developing an orange-pink color. Discharge around it clears up and the crypts become more prominent. Microscopic studies show no demonstrable change in such lymphoid tissue or in the nasal polyps.

The changes in the nose and nasopharynx regress after discontinuing therapy. Within a few days the nasal mucosa loses its dusky appearance, and the lymphoid tissue returns to its former state. Nasal polyps return in from two weeks to two months.

Cortisone therapy has very much the same effect on the tissue of the respiratory tract, except that no marked color change was noted in the nasal mucosa or in the nasopharyngeal lymphoid tissue in the patients under such treatment. Nasal sprays of cortisone have resulted in a slow but definite regression of nasal polyps.

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THE EFFECT OF ADRENOCORTICOTROPIC HORMONE (ACTH) AND CORTISONE ON THE COURSE OF DISSEMINATED LUPUS ERYTHEMATOSUS AND PERIARTERITIS NODOSA

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INTRODUCTION

The beneficial effects of adrenocorticotropic hormone (ACTH) and cortisone in patients with disseminated lupus erythematosus have been described by several groups of observers during the past year (1–5). In the present communication the experience gained during the last twelve months in the treatment of eight such patients with ACTH and four with cortisone will be presented. In addition, five patients who had extensive cutaneous lesions without any outstanding systemic manifestations have been observed, four of whom were given ACTH and one cortisone. The diagnosis was straightforward in each instance, and the evaluation of the clinical results to date will be based on a recent analysis of thirty-two proven untreated cases seen in recent years in this hospital (6). One case of florid periarteritis nodosa has been followed with serial biopsy studies, and the effect of ACTH on the anatomical lesions will be presented.

In general, the results have been very encouraging with both ACTH and cortisone. Complete remissions lasting up to eleven months have followed a single course of treatment. Two patients have died. Therapy in one of these was inadequate and had to be discontinued because of complicating infection. In the other adequate therapy could not be given because of severe renal insufficiency. In the patients with chronic cutaneous lesions but without systemic manifestations, the results thus far have been less impressive.

MATERIAL

In Tables 1 and 2 are presented in outline form the clinical manifestations presented by each patient was well as the important laboratory findings. The blood of nine of the patients with disseminated lupus

TABLE 1

Cases of Active Dissemination Lupus Erythematosus Treated with ACTH and Cortisone

CASE AGE SEX RACE	DATE ONSET DISEASE	CLINICAL MANIFESTATIONS							LABORATORY TESTS							TREATMENT				IMMEDIATE RESULTS	FOLLOW-UP
		Fever	Weight loss	Skin lesions	Arthritis	Other serous memb.	G.G.E.	Renal	Sed. rate/mm./hr.	Hematocrit	WBC thous.	EOS count	Platelets thou.	Globulin gm. %	L.E. cells	Date begun	Initial dose	Total dose (ACTH) (C)	No. days		
(1) G. P. 501114 47 M W	Aug. 1948	+	+	−	+	+	−	−	29	40.2	6.3	55	N	1.7	+	June 9 1949	100	1113 (ACTH)	59	Prompt response of fever, arthritis, sed. rate. Lost weight during treatment, then gained. Post-treatment rise in eosinophils	No return of activity after 11 months. Feels perfectly well and at work
(2) H. R. 508063 33 M W	Aug. 1948	+	+	+	+	+	−	+	30	33	2.1	33	N	3.0		July 27 1949	75	1532 (ACTH)	45	Prompt response of fever, arthritis, sed. rate. Relapse as dose tapered, second remission as dose raised, then rebound with spontaneous remission	Active and at work after 7 months, with no clinical relapse
(3) G. P. 514072 37 M W	Mar. 1948	+	+	+	+	+	+	+	33	35.4	4.5	88	N	5.7		Sept. 20 1949	69	2031 (ACTH)	68	Prompt response of fever, chest pain, arthritis, sed. rate. Complicated by staphylococcus septicemia during treatment. Developed thrombophlebitis	Transient fever, weakness, pain Jan. 1950. No treatment. No active clinical manifestations after 10 months
(4) H. F. 527492 40 F W	Dec. 1949	+	+	+	−	−	+	−	29	35	7.9	66	N	2.7	+	Feb. 18 1950	100	835 (ACTH)	15	Promptly afebrile, G.G.E. subsided, sed. rate normal. L.E. cells still present, when dose tapered developed transient angioneurotic edema. Rebound after treatment with spontaneous remission. Fever and arthralgia during rebound	Well except for transient urticaria until July 8, 1950, when lymph node enlargement in neck noted and began to have mild fever
(5) M. E. 485050 21 F W	Dec. 1946	+	+	+	+	−	−	+	38	32	10.0	55	N	3.3	−	Dec. 12 1949	140	922 (ACTH)	24	Prompt response fever and arthritis. Slower healing cutaneous lesions. N.P.N. elevated and rose during treatment. Rebound after treatment with fever, arthritis, followed by spontaneous remission. N.P.N. fell to pretreatment level	Occasional arthralgia until May 16, 1950, when arthritis reappeared and renal failure progressed. Treated July 6. Fever subsided, died in uremia

(6) H. P. 479526 16 F W	Dec. 1947	+	−	+	+	+	−	−	30	35	8.6	66	N	9.4		July 30 1949 Nov. 23 1949	100 100	1573 (ACTH) 625 (ACTH)	27 15	Fever and arthritis subsided promptly. Globulin dropped to 3.1. Sed. rate unchanged. Mild rebound with fever which subsided spontaneously. Oct. 21 began to run fever and have some joint symptoms. Responded well to second course ACTH but had severe rebound with high spiking fever and arthritis which subsided spontaneously over 6 days	Ambulatory, essentially afebrile and no active joint symptoms at last report in June 1950
(7) M. G. 526120 18 F W	Jan. 1945	+	−	+	+	+	−	−	30	34	2.5	33	N	3.0	+	Feb. 8 1950	100	915 (ACTH)	18	Excellent response of fever, arthritis, cutaneous lesions, sed. rate. Transitory aching of joints in immediate post-treatment period	Well for 4 months, when had return of fever, arthritis, butterfly eruption. Second course treatment begun July 18, 1950
(8) M. R. 505022 32 F W	May 1942	−	−	+	+	+	−	−	8	31	5.6	132	30		+	May 23 1950	100	3040 (ACTH)	29	Slight reticulocytosis during treatment and hematocrit returned to normal but there was no change in the thrombocytopenia	
(9) O. G. 532488 37 F W	Feb. 1950	+	+	+	+	+	−	−	30	26	10.0	165	N	2.3	+	Mar. 30 1950	400	2425 (C)	14	Prompt subsidence of fever, arthritis, cutaneous lesions, subcutaneous nodules. Transitory urticaria as dose dropped below 75 mgm. Sed. rate became normal	Still well 3 months after treatment with no evidence of recurrence
(10) L. D. 532508 19 F C	Feb. 1950	+	+	+	+	−	+	+	36	28	2.0	10	N	5.8	+	Mar. 30 1950	400	2650 (C)	15	Prompt fall in temperature with subsidence of skin lesions. Developed convulsions and hemiplegia during treatment, probably due to disease process and not treatment as they recurred several months after therapy	Remained afebrile with mild cutaneous lesions, leucopenia, elevated sed. rate. July 1 had convulsion and second course treatment started
(11) A. G. 495127 36 F W	Oct. 1948	+	+	−	+	+	+	−	34	32	4.6	60	N	4.1	+	Apr. 10 1950 May 12 1950	300 300	1800 (C) 1575 (C)	18 13	Prompt fall in temperature and subsidence of arthritis. Relapsed day after first course. Retreated with good results but had return of fever and arthritis seven days later	
(12) I. M. 521688 47 F W	July 1948	+	+	+	+	+	+	+	32	35	2.3	11	N	5.3	+	Dec. 2 1949	100	1100 (C)	11	Temperature returned to normal and leucocytes rose to 16,000. Otherwise no striking change. 8th day developed empyema necessitatis. Granulation tissue did not form in wound	Died 4 weeks after inadequate cortisone therapy

TABLE 2

Cases of Lupus Erythematosus with Cutaneous Lesions as the Only Clinical Evidence of Active Disease at Time of Treatment with ACTH or Cortisone

CASE AGE SEX RACE	DATE ONSET DISEASE	CLINICAL MANIFESTATIONS	LABORATORY TESTS					TREATMENT				RESULTS
			Sed. rate/mm./hr.	Hematocrit	WBC thou.	EOS per cu. mm.	L.E. cells	Date begun	Initial dose	Total dose (ACTH) (C)	No. days	
(13) H. N. 526560 30 F W	Jan. 1947	3 years before admission migratory polyarthritis. Cutaneous lesions for 8 weeks involving butterfly area, ears, neck, fingers, palms. Skin biopsy showed characteristic picture. Occasional mild arthralgia	6	40	4.3	44	+	Jan. 22 1950	200	2050 (C)	17	Prompt clearing of all cutaneous lesions. Since treatment occasional transient isolated lesion on face. Last follow-up 6 months after therapy
(14) B. S. 510202 43 F W	Jan. 1949	Skin always rather sensitive to sunlight. 14 weeks before treatment developed typical lesions on hands, neck, arms, and later on face after exposure to sunlight. Biopsy of skin confirmed diagnosis	17	44	4.3	57		Aug. 17 1949	100	1780 (ACTH)	38	Gradual clearing of lesions (see photo). Mild relapse after treatment and mild transient lesions for several weeks. Since then to last follow-up 10 months after therapy skin has been essentially normal
(15) E. C. 510303 63 F W	Dec. 1948	8 months before treatment developed lesions on face, arms, and legs accompanied by loss of weight. Biopsy showed characteristic lesions	32	44	3.9	99		Aug. 23 1949	100	1100 (ACTH)	29	Skin improved an estimated 50% during treatment. Mild relapse immediately with gradual return to level obtained under therapy. Maintained this improvement for 8 months (time of last follow-up)
(16) K. L. 464514 36 M W	Jan. 1942	8 years before therapy developed facial lesions exacerbated by sunlight. Severe chronic involvement of face, arms, legs, collar area. Biopsy showed characteristic lesions	26	49	5.5	110	−	Feb. 19 1950	100	2130 (ACTH)	17	Some temporary improvement in lesions during treatment with return to essentially the pre-treatment level after therapy stopped
(17) M. T. 536620 30 F W	May 1945	5 years before had polyarthritis and eruption over butterfly area. Subsided after a few weeks. 8 weeks before treatment had reappearance of florid skin lesions involving face, neck, collar area, arms. Biopsy showed characteristic lesions. (See photo)	33	32	4.6	0	+	May 10 1950	100	1042 (ACTH)	17	Excellent response of skin lesions during therapy. Sed. rate remained elevated. 5 days after therapy erythema reappeared. 3 weeks later skin lesions developed again and she had a daily rise in temperature

was examined for the "L.E." cells of Hargraves and they were found in all but one case. The diagnosis was confirmed by biopsy of a lymph node in one and of cutaneous lesions in two others. In all five patients with cutaneous lesions but without systemic manifestations, biopsy of the skin showed the typical picture; and in two of three studied "L.E." cells were found in the blood.

In the patients with active disseminated lupus the clinical picture was in general entirely similar to that seen in previous years. All of the patients but one (case 8) had fever at the time of admission as well as active arthritic manifestations. Seven of the twelve had cutaneous manifestations at the time treatment was begun, while four others had previously had skin involvement. There was involvement of the pleura in eight and of the pericardium in three. Generalized lymph node enlargement was noted in six. All but two had lost weight and there was evidence of renal damage in five, although only cases 5 and 10 had azotemia.

There was a mild to moderate degree of anemia in twelve and a white cell count below 5,000 per cu. mm. in seven. Only one had a significant degree of thrombocytopenia, and this was the only case in which the sedimentation rate was not elevated. Five patients had a serum globulin above 4.0 gms. per cent, the highest being 9.4 and the lowest 1.7.

Most of the patients had received a variety of other types of therapy without any effect on the course of the illness. Therapy with several antibiotics was tried without success in all cases who had fever, although all bacteriological studies were normal.

The average duration of the disease in these cases before therapy with ACTH or cortisone was begun was 24 months, with a maximum of 96 and a minimum of one. In all instances but one the patients were seriously ill with active disease at the time of treatment. In case 8 there was thrombocytopenia with bleeding and joint pains but no fever. In three cases the disease was of the acute fulminating type with onset less than two months before therapy. In the others there had been fluctuations in the severity of the activity, and in a few almost complete spontaneous remissions for periods up to three months. In the cases previously reported from this clinic the average time from onset of symptoms to death in 26 patients was four years and four months.

Many patients will live for very much longer periods of time and the tendency to remission and exacerbations is quite marked in a large number. This fact must be considered in the evaluation of any treatment, and the period of observation must be lengthy before any final conclusions can be drawn. The material in the present study seems excellent as there is a good division between chronic cases with periods of remission and severe relapse and those of the acute fulminating type of recent onset.

For purposes of description five patients (Table 2) who had diffuse cutaneous manifestations as the most striking feature at the time of treatment have been placed in a separate category. None of these patients had any noteworthy systemic manifestations at the time of admission, but, as one reviews the course of the illness there can be little doubt that three (cases 13, 16, 17) had disseminated lupus erythematosus. However, the dominant abnormality to be followed under treatment was the dermatological picture. None had fever or active serous membrane involvement, although all but one had elevation of the sedimentation rate, four had a white cell count below 5,000 per cu. mm. and in two "L.E." cells were found in the peripheral blood.

TREATMENT SCHEDULES

It is quite obvious from the data in Tables 1 and 2 that no uniform treatment schedule was followed. The duration and amount of treatment varied with the response of the patient, the amount of drug available, and a desire to explore for the most satisfactory program. The total dosage of ACTH employed varied from 835 mgm. (Armour standard) to 3040 mgm. and the duration of treatment from 15 to 68 days. In most instances the initial daily dose was 100 mgm. gradually reduced to 20 or 10 mgm. In several instances a daily dose of 10 mgm. per day was continued for a month. Each daily dose was divided and given at six-hour intervals. Typical examples of the treatment schedules will be found in Charts 1, 2 and 3. In two instances two courses of ACTH were given with an interval of a few days between.

In the cases treated with cortisone the total dosage varied from 1100 mgm. to 2650 mgm. and the duration of treatment from eleven to 18 days. The initial dose was in most instances 200 to 400 mgm. Toward the end of the treatment period there was a gradual lowering of the

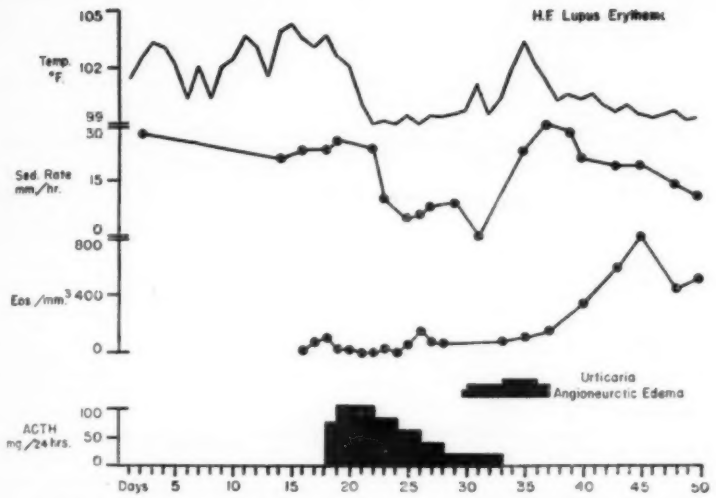

Chart 1: Case 4. Disseminated lupus erythematosus treated with ACTH. There was a prompt fall in temperature with drop in the sedimentation rate to normal. At the end of treatment she developed the Rebound Phenomena with fever and rise in the sedimentation rate. Remission took place without further treatment.

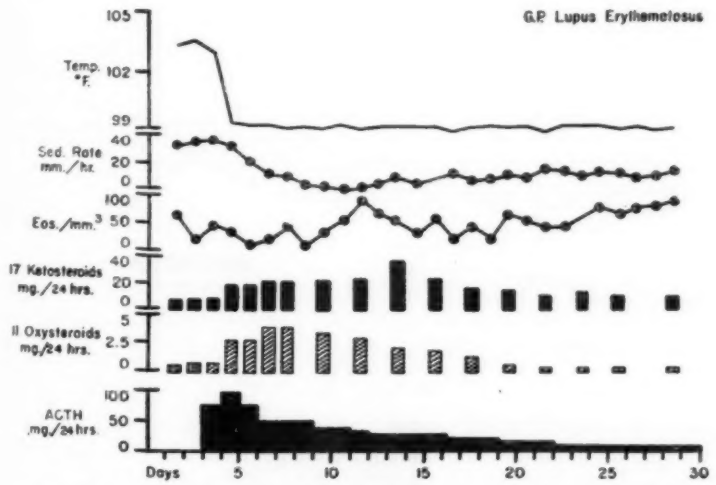

Chart 2: Case 1. Disseminated lupus erythematosus treated with ACTH. The eosinophil count fluctuated during treatment, but there was a prompt rise in the urinary excretion of 17 keto and 11 oxysteroids.

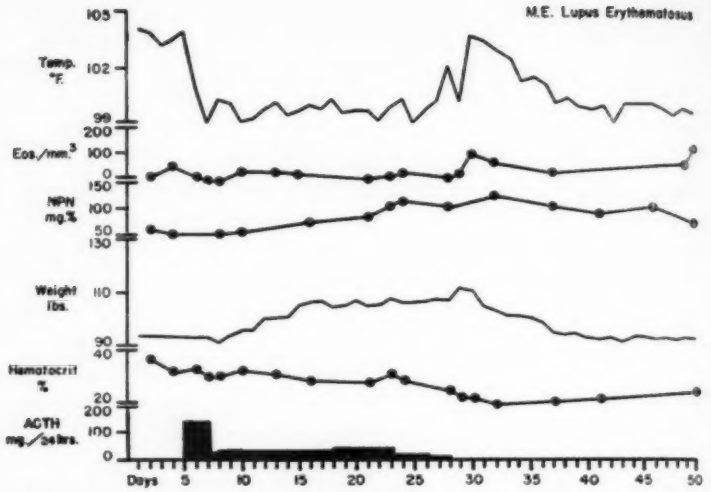

Chart 3: Case 5. Disseminated lupus erythematosus treated with ACTH. Note the Rebound Phenomenon which spontaneously subsides. This patient had renal insufficiency with rise in the NPN and marked weight gain during treatment.

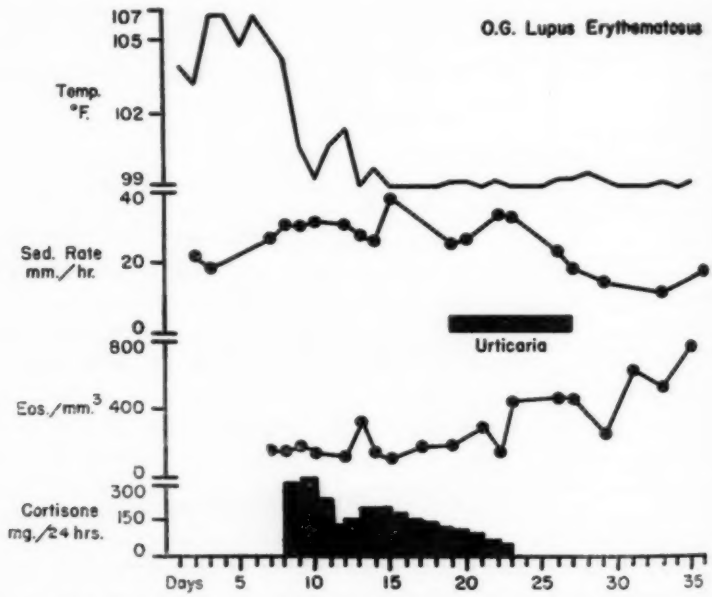

Chart 4: Case 9. Disseminated lupus erythematosus treated with cortisone. This patient developed urticaria toward the end of the treatment period. Note the delayed fall in the sedimentation rate and the steady rise in the eosinophil count.

dose. In one instance a second course was given because of an immediate recurrence of active symptoms. Chart 4 shows the dosage schedule in case 9. The response did not seem to vary if the daily dose was given in a single injection or divided into equal parts and given at 6 to 12 hour intervals.

RESULTS

General

a. *The cases of active disseminated lupus:* In each instance there was an immediate and dramatic response to both cortisone and ACTH when given in adequate doses. The temperature was normal and the joint pains disappeared within 24 hours. The patients rapidly developed a sense of well-being with loss of the feeling of fatigue and a striking increase in appetite. Case 3 had such severe muscular and pleural pain that he could not be touched or moved in bed and was requiring demerol in large doses. Within a few hours pain was absent and demerol administration was stopped without difficulty. Sweating accompanied the defervescence in many instances and the dramatic improvement resembled in its rapidity the spontaneous crisis in lobar pneumonia. In three instances the dose was tapered too rapidly with a mild recurrence of fever and joint pains. These manifestations quickly subsided when the daily amount of cortisone or ACTH was increased. In two instances there was, within a few days after a course of treatment, a recurrence requiring further therapy, one with cortisone and the other with ACTH.

In four cases there has been no significant clinical relapse after a single course of therapy:

Case 1: This patient had constant fever and arthritis with elevation of the sedimentation rate for eleven months before therapy with ACTH. He was clinically well 24 hours after treatment was started, and the sedimentation rate became normal on the fourth day. He has remained completely well for the ensuing eleven months.

Case 2: This patient had had active disease for eleven months with fever, arthritis, pleuritis, pericarditis, cutaneous lesions and elevation of the sedimentation rate. He was confined to bed during this entire period. During a period of seven months since treatment, he has remained afebrile, and has carried on a photographic business. There is still atrophy of the muscles about the joints which were involved, he has not reached his normal weight, but has only occasional transient arthralgia.

Case 3: This patient had been critically ill for 17 months with fever, arthritis, cutaneous lesions, pleuritis, and nephritis. Pain was so severe that he had received large doses of demerol for several months. His immediate response to treatment was dramatic but he developed a staphylococcal septicemia and extensive thrombophlebitis during the period of ACTH administration. After ten months he is still underweight and has edema of the legs as a consequence of the thrombophlebitis. He is afebrile, does part-time work as a chemical engineer and has no clinical evidence of active disease.

Case 9 had been acutely and critically ill for six weeks with high fever, cutaneous lesions, arthritis, and extreme prostration. She responded dramatically to cortisone therapy and is still completely well three months later.

Five cases have had relapses of varying severity from seven days to four months after treatment. Two of these have received additional therapy. One relapsed again after seven days and the other has shown no further clinical evidence of active disease during a period of six months.

Case 4: This patient had had attacks of urticaria and angioneurotic edema for many years. Two months before treatment she developed high fever and generalized lymph node enlargement. Lymph node biopsy showed the characteristic lesions of disseminated lupus erythematosus. During ACTH administration she became afebrile, and the adenopathy completely subsided. She was well for almost five months, at which time cervical adenopathy reappeared and she developed a low grade fever. She is at present in the hospital for further study and treatment if indicated. The adenopathy is much less marked than originally, and the temperature at a very much lower level than prior to the initial course of treatment.

Case 7: This patient had had active disseminated lupus erythematosus of fluctuating severity for a period of five years. During ACTH therapy she had a complete remission with subsidence of fever, arthritis and cutaneous lesions. The sedimentation rate dropped but did not remain at a normal level. Four months later she had a return of the same active manifestations of the disease and is now receiving a second course of therapy.

Case 6: This patient who had had the disease for eighteen months responded well to ACTH administration with subsidence of fever and arthritis and a fall of the serum globulin to a normal level. The sedimentation rate remained elevated. Ten weeks later fever and arthritis reappeared and the globulin had reached its previous high level. Her response to a second course of ACTH was prompt, although she had high fever and arthritis for seven days after termination of therapy. For the following seven months she has been ambulatory and afebrile with no clinical manifestations of disease activity.

Case 10: This patient had an acute fulminating type of disseminated lupus of only four weeks duration, characterized by high fever, arthritis, angioneurotic edema, generalized lymph node enlargement and nephritis. The immediate response to cortisone was excellent but as the dose was being tapered she developed convulsions followed by a hemiplegia. There was a gradual return of function and she was afebrile, without active arthritis but with some residual angioneurotic edema for a period of almost three months. During this time the sedimentation rate remained elevated. Fever then returned, she again had convulsive episodes and is at present receiving further treatment.

Case 11: The onset of the disease in this case antedated treatment by eighteen months and was characterized by high fever, loss of weight, asthenia, arthritis, pericarditis and elevation of the sedimentation rate. She received two courses of cortisone therapy with excellent immediate response but with return of fever and active joint manifestations within seven days after cessation of therapy. The sedimentation rate remained elevated.

Two cases in this series have died, one as a consequence of bacterial infection and the other as a result of renal insufficiency.

Case 5: This patient had had active disseminated lupus for three years with recurrent episodes of polyarthritis. Two weeks before treatment she developed a high fever and in addition to arthritis and cutaneous lesions had a severe nephritis with renal insufficiency. The fever, arthritis and skin lesions subsided during therapy with ACTH but the azotemia increased and she received only 922 mgm. over a 24 day period. After cessation of therapy the non-protein nitrogen fell to pretreatment levels. The sedimentation rate remained elevated. She was readmitted four months later with the same clinical manifestations but with a much more advanced degree of renal insufficiency. The administration of ACTH resulted in subsidence of the fever and arthritis but her renal function did not improve and she died in uremia.

Case 6: This patient was extremely debilitated as a result of severe lupus erythematosus over a period of 18 months. This was the first patient treated with cortisone and 100 mgm. was given for 11 days, a total dose of only 1.1 gm. Toward the end of this period she developed empyema necessitatus, cortisone administration was stopped and she died a few weeks later as a result of the infection.

b. *Cases with Predominantly Cutaneous Lesions:* The overall results have not been as satisfactory in this group of patients. In those patients who had chronic lesions of over eight months' duration (cases 15 and 16) there was some temporary improvement judged at 40 to 50 per cent but relapse occurred shortly after termination of therapy, although one patient (case 15) feels the lesions are not as extensive nine

months after treatment with ACTH as previously. Two of the patients with lesions of recent onset have remained essentially well, but one relapsed within two weeks of termination of therapy. Four of these patients were treated with ACTH and one with cortisone. In all instances the diagnosis was confirmed by biopsy of the skin before therapy was instituted.

Case 17 had had an attack of acute disseminated lupus five years previously. For two months prior to treatment she had had the typical cutaneous lesions of the disease over the face, neck, ears, and hands (Fig. 1, 2). There was no febrile

Figure 1: Case 17. Lupus erythematosus treated with ACTH. Left, photograph taken before treatment. Right, photograph taken at the end of the treatment period.

reaction but the white cell count was 2,560 per cu. mm. and the sedimentation rate 35 mm./hr. She received a total of 1031 mgm. of ACTH (Armour) over a period of 17 days. The lesions on the face showed rapid disappearance of edema, erythema, and crusting. At the end of the course of therapy only slight erythema and some thickening of the skin over the neck remained (Fig. 1, 2). The sedimentation rate did not change and two weeks after therapy the lesions were returning with moderate rapidity.

Case 14 had had no history of active disseminated lupus but the sedimentation rate was elevated and the white cell count 4.3 thousand. Fourteen weeks before admission she developed maculo-papular lesions over the hands which spread to

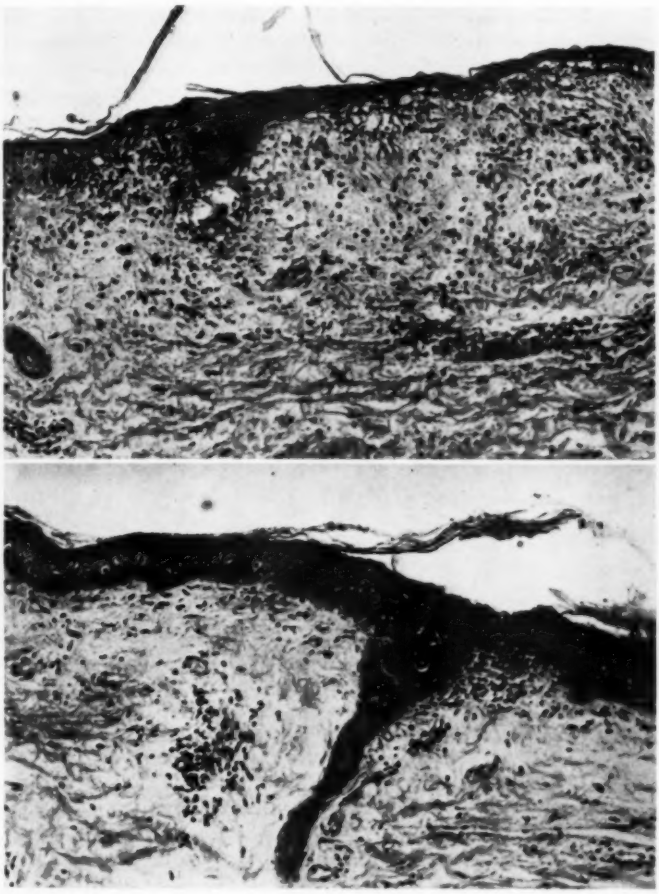

Figure 2: Case 17. Lupus erythematosus. (Derm. Path. 8486—1 and 2.) Biopsies of skin:

Upper) Before treatment. There is atrophy of the epithelial layer and vacuolization at the juncture between the epithelium and the corium. Note the mononuclear cell infiltration of the corium.

Lower) Nine days after beginning treatment with ACTH. The epithelium is now normal in appearance. The mononuclear cell infiltration is less marked.

the arms. Extensive lesions later appeared over the face and neck. The cutaneous manifestations were classical and the diagnosis was confirmed by biopsy. There was essentially complete healing under ACTH therapy which consisted of a total of 1790 mgm. over a period of 38 days (Fig. 3). After cessation of therapy there was a temporary relapse following which the lesions spontaneously improved. It was thought this was similar to the rebound phenomenon seen in other cases. About one month later she had a temporary mild exacerbation but for the nine months has been completely well.

Case 16 had had the cutaneous lesions of lupus, fluctuating in severity, for a period of seven years. At the time of admission there were extensive and very advanced dermatological changes, involving the face, arms and trunk. The diag-

Figure 3: Case 14. Lupus erythematosus treated with ACTH. Left, photograph taken before treatment. Right, photograph taken three days after termination when mild relapse had occurred. This was followed by a spontaneous remission.

nosis was confirmed by biopsy and the only other abnormality was a moderate elevation of the sedimentation rate (25 mm./hr.). He received a total of 2130 mgm. of ACTH (Armour) over a period of 18 days, the daily dose being as high as 150 mgm. The erythema faded almost completely and large islands of normal appearing skin were present. When the dose was reduced below 100 mgm., however, the lesions gradually reached their original intensity and distribution.

Case 15 had had severe cutaneous lupus involving the face, upper trunk, arms and lower legs for a period of eight months. The diagnosis was confirmed by biopsy and the only other abnormalities were a white cell count of 3.9 thousand and a sedimentation rate of 32 mm./hr. She received a total of 1910 mgm. of ACTH over a period of 30 days. The lesions improved an estimated 50% and her condition has remained stationary in the eight months since therapy was discontinued. This patient also had a slight exacerbation as the dose was lowered but then spontaneously improved.

Case 13, who had classical cutaneous lupus involving the face and hands, was treated with cortisone with a prompt and complete response which has been maintained. In the four months since termination of therapy, there has been an occasional small transient lesion on the face. She received 2050 mgm. of cortisone over a period of 18 days.

Effects on certain specific manifestations of the disease

Fever: One of the most dramatic evidences of the clinical response was the rapid return of the temperature to normal. There was a significant degree of fever in nine patients which had been a prominent and continual part of the active disease for an average of 15 weeks before admission, ranging from two to fifty-two weeks. The maximum daily temperature ranged from 101.8 to 106°F (rectal). Following the initiation of ACTH therapy in five patients, the temperature fell to normal within eight to forty-eight hours. In four cases given cortisone the patients were afebrile in an average of 33 hours with a range of 20 to 48 hours.

Joint Manifestations: Active joint manifestations with pain and swelling were present at the time of treatment in six patients who received ACTH and in four who were given cortisone.

In almost every instance active pain and joint tenderness subsided within four to twelve hours after ACTH therapy was begun, and movement was greatly enhanced. Complete disappearance of periarticular swelling usually required several days.

In the patients treated with cortisone the abatement of these manifestations usually took place in three to four days.

More chronic joint changes disappeared with amazing completeness and after a few weeks mucular atrophy was much less evident. Figure 4 shows the rather remarkable degree to which changes present for a year or more can subside.

Cutaneous Manifestations: Of the 12 patients with active disseminated lupus, eight had some type of cutaneous lesion at the time treatment was instituted. Six had the characteristic "butterfly" lesions over the nose and malar eminences, four had the typical erythematous lesions about the nail beds, three had changes resembling erythema nodosum, two had angioneurotic edema of the eyelids and face, one had urticaria, and one had firm subcutaneous nodules. In most instances these changes had been of recent onset, none being of more than a few weeks' duration. All of these manifestations receded within a few days

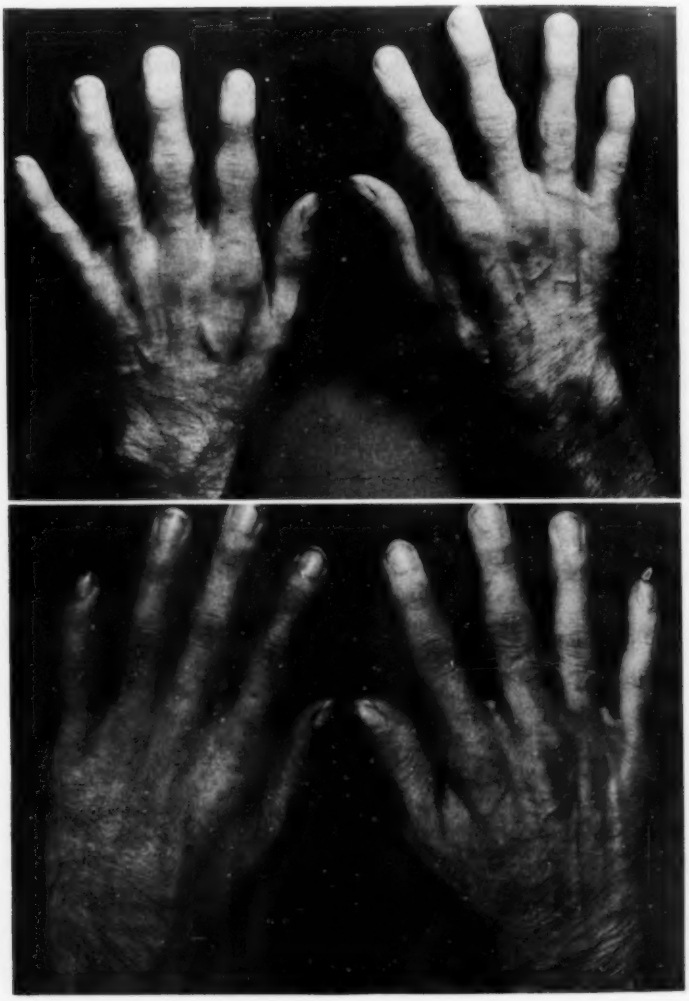

Figure 4: Case 2. Disseminated lupus erythematosus. Upper photograph shows the arthritic changes in the hands before treatment. Lower photograph shows the condition of the hands at the end of the treatment period.

after treatment with either ACTH or cortisone was started. The response paralleled rather closely the disappearance of joint and periarticular swelling. Two patients developed urticaria and angioneurotic edema toward the end of the treatment period when the dosage had been reduced to a low level. In each instance the patient had received antibiotic therapy in the pretreatment period. It is possible that they had developed to the antibiotic a hypersensitivity reaction, the manifestations of which were suppressed by the higher doses of cortisone and ACTH.

Involvement of the Other Serous Membranes: Two patients had evidence of active pleuritis at the time of therapy. Pain and limitation of motion were present without accumulation of fluid. In both instances the symptoms were abolished within 24 hours after beginning treatment.

In case 11 there was a loud pericardial friction rub present at the time cortisone therapy was started. On the second day it had decreased greatly in intensity and extent and on the fourth day could no longer be heard. On the tenth day of treatment when the dose had been reduced to 50 mgm. the patient complained of precordial tightness and the friction rub was again audible for one day, but at this time there was evidence of an accumulation of fluid in the pericardial and right pleural cavities. There was a gradual subsidence of these manifestations during a second course of cortisone therapy.

Renal Manifestations: Case 5 (Chart 3) was the only patient who had severe renal damage as a result of disseminated lupus. There was mild hypertension with elevation of the non-protein nitrogen to 60 mgm.%. The phenolsulfonphthalein excretion was 50% in two hours; there was reduced ability to concentrate the urine, and albuminuria with numerous red cells and casts were present. During treatment she gained weight rapidly, became edematous, the blood volume increased and cardiac insufficiency resulted. The non-protein nitrogen level rose to 100 mgm.% and the albuminuria increased. After ACTH administration was stopped she regained her normal weight and the non-protein nitrogen fell to its pre-treatment level. However, renal function became progressively poorer and she died in uremia a few months later. In case 10 there was albuminuria with a few red cells and casts in the urine. During treatment she developed massive edema and the non-

protein nitrogen level rose from normal to 57 mgm.%. After treatment with cortisone was stopped, the edema subsided and the non-protein nitrogen returned to normal but albuminuria and microscopic changes persisted. In three of the other cases (2, 3, 12) there was albuminuria, microscopic hematuria and cylindruria which were not altered during treatment.

Effect on Other Manifestations: Coincident with clinical improvement the patients lost their feeling of drowsiness, malaise and asthenia. The appetite rose to voracious levels and a mild euphoria developed which seemed to parallel the degree of clinical improvement. Patients who felt weak and depressed as a result of the serious illness and confinement to bed usually commented upon the rapid appearance of a sense of well-being and strength.

There was evident lymph node enlargement in five of the patients and a rapid disappearance of the palpable nodes was recorded in each instance.

In only one patient was any important neurological abnormality noted. Case 10 developed a marked euphoria on the second day of cortisone therapy. Her behavior over the next few days became maniacal and she developed auditory hallucinations. Cortisone was discontinued but the psychotic reaction continued and she developed a hemiplegia and convulsive episodes. There was gradual recovery until three months later when there was a return of the convulsive attacks. It seems likely that these manifestations were due to involvement of the central nervous system by the disease itself rather than a primary result of the therapy. She is now being treated again with cortisone and has had no recurrence of mania or convulsions.

The Rebound Phenomenon: In five of the patients with active disseminated lupus, there has occurred, when the dose of ACTH was reduced below 40 mgm. per day a temporary relapse which has subsided spontaneously in each instance and has been designated as a rebound phenomenon. It was characterized by a rise in temperature reaching as high as 104° in some instances and gradually subsiding over a period of from seven to fifteen days. In three patients this febrile episode has been accompanied by a return of arthralgia and joint stiffness of moderate severity. One patient had urticaria and angioneurotic edema during this period and another developed tender reddish subcutaneous nod-

ules. In three patients there was a sharp rise in the sedimentation rate which had been normal when the relapse began. In two the rate was high at the time and did not change, while in another it remained normal. In all but one patient there was a sharp rise in the eosinophil count following the reduction in ACTH dosage, usually to much higher levels than existed prior to the start of treatment. This phenomenon has not as yet been encountered in the few patients treated with cortisone. Typical examples are presented in charts 1 and 3. This type of reaction is of practical importance as it points out the fact that if signs of activity appear toward the end of what is believed to be a reasonably adequate course of therapy, it may not be necessary to resume treatment immediately at a higher dosage level.

Hematological Studies: Eleven of the total series of patients had a white cell count below 5,000 per cu. mm. during the pre-treatment period of observation, the average value being 3,320 with a range of 2.1 to 4.6 thousand. This average rose during treatment to 6,820 with a range of 5 to 12.4 thousand. Taking the lowest counts during the two week period after cessation of therapy, the average value was 4,630 with a range of 2,850 to 6,600. In only three patients did the white cell count remain above 5,000 per cu. mm. There were six patients who had white cell counts in the pre-treatment period between 5.0 and 10.0 thousand with an average count of 6,230. The average maximum count in this group during treatment was 15,330 with a range from 10,500 to 21,900. The count fell in the post-treatment period to an average of 5,840 varying from 4,900 to 7,000. In those patients with an initial leucopenia the average percentage rise in total white cell count was 51 as compared to 60 in the cases starting with a normal count.

The neutrophilia which follows the administration of ACTH and cortisone was evident in these cases. There was no significant difference in the rise in neutrophils seen in those patients with normal as opposed to low total white cell counts in the pre-treatment period. In those cases with initial leucopenia the average neutrophil count was 65%, rose to 91% during, and fell to 76% in the post-treatment period. The corresponding figures for the group with a normal total count were 71%, 86%, and 66%. The usual lymphopenia which results from ACTH and cortisone was evident in all of the cases but three during the time the hormones were being administered.

Many of these patients had some degree of anemia which was usually normocytic in type. The effect of treatment on this abnormality is difficult to evaluate as metabolic and other studies necessitated the withdrawal of sizable quantities of blood during the treatment period. The average hematocrit value in the entire series at the time of treatment was 34.3% with a range of 26 to 44. Taking the maximum value reached in the immediate post-treatment period, this average rose to 39%. The effect on the anemia can be more clearly seen if one considers the eight cases who had hematocrit reading below 35% at the time of treatment. The average pre-treatment value in this group was 31.5% and rose to 38.5%. In a few patients there was a very impressive response as in Case 9 whose initial hematocrit value of 26 rose to 45%, and Case 8 where the change was from 29 to 41.5. In both of these patients there was a mild reticulocyte response to 2 to 3% but in no instance any more apparent evidence of blood regeneration. None of these patients was transfused during the treatment.

Sedimentation Rate: Fifteen of the patients, including those with predominant cutaneous lesions, had an elevation of the sedimentation rate (Wintrobe) at the start of therapy with an average value of 30 and a range of 17 to 36 mm/hr.

Eleven of these patients were treated with ACTH and the sedimentation rate fell to normal in seven in an average of ten days with a range of five to 21 days. In the other four there was no change from the pre-treatment value. Cases 16 and 17 both had cutaneous lupus without fever and the lesion relapsed rather rapidly after cessation of therapy. In the two patients with active disseminated lupus whose sedimentation rate did not change (Cases 7 and 6), one relapsed in three months and the other had only a partial clinical remission after each of these courses of ACTH.

Case 9 was treated with cortisone and the sedimentation rate fell to normal in 25 days. Three other patients whose rate was elevated and who were treated with cortisone showed no variation from the pre-treatment value. One was inadequately treated (Case 12) and the other two had a prompt relapse after the therapy was discontinued.

The Eosinophil Count: The eosinophil count was not satisfactory as a guide to the dosage of ACTH as there were in most instances few or none of these cells present during the pre-treatment period. In all

instances in which ACTH was administered the eosinophil count remained at low levels or no cells were found during the treatment period when the daily dose was above 30 mgm. It is of some interest to compare the highest count in each patient in the pre- and post-treatment period. The average count in the pre-treatment period, taking the maximum of several values, was 80, with a range of 11 to 276. Taking the highest of several values in the second and third weeks of the post-treatment period, the average of all cases was 204 with a range of 11 to 880.

The "L.E." Cells of Hargraves: Hargraves (7) first reported the occurrence of a peculiar type of cell in the bone marrow of patients with disseminated lupus erythematosus which he has designated as the "L.E. cell". Subsequent studies revealed that these cells could be demonstrated only in marrow which had been treated with an anticoagulant. The cells were also detected in the peripheral blood of patients with this disease when it was similarly treated. Hargraves (8) and Haserick and Bortz (9) have observed these cells in normal marrow incubated with plasma from patients with disseminated lupus erythematosus. The substance which seems necessary to cause the formation of "L.E. cells" is associated with the gamma globulin fraction of the serum (10). In the studies reported to date these cells have not been found in blood from patients with a variety of other diseases and are believed to be specifically associated with disseminated lupus erythematosus, disappearing during periods of spontaneous remission. Hench et al. (4) and Thorn et al. (2) have observed the disappearance of these cells from the blood during treatment of patients with ACTH.

The peripheral blood has been examined for these cells in 12 and the bone marrow in 10 patients reported in this series. 0.1 ml. of a solution of sodium heparin (10 mgm. per ml.) was dried in a glass test tube and 5 ml. of blood or 1.0 ml. of aspirated bone marrow added. After a period of incubation the blood or marrow specimen was transferred to an hematocrit tube and centrifuged for 10 minutes at 2000 r.p.m. The buffy coat was withdrawn with a capillary pipette and thin smears made on cover slips. These were stained with Wright's stain and examined. Extremely few L.E. cells may be found and in each instance careful and intensive search was made of several cover slip preparations before a negative report was recorded.

In 85 preparations from patients with a wide variety of diseases

other than disseminated lupus erythematosus no "L.E. cells" could be found. In 10 of the 12 patients with disseminated lupus erythematosus these cells have been demonstrated. In each instance they were found in the peripheral blood and also in the bone marrow in nine of the ten studied.

TABLE 3

Serum Protein Pattern and Complement Titre (Case 6)

Total serum protein gms./100 ml.	10.2			10.4	10.9					10.4				9.5			9.4	9.4		
Globulin gms./100 ml.	7.8			8.0						7.1				6.7			6.1			
Albumin gms./100 ml.	2.4			2.4						3.3				2.8			3.3			
Electrophoretic analysis % each component																				
1					19															25
2					3					(Component 1 albumin)										3
3					3					(Component 6 gamma globulin)										7
4					0															8
5					10															12
6					65															45
Complement titer arbitrary units/ml.	22	19		19	22			29	36		32		33	33						32
ACTH mgm./24 hrs.						21	84	84	63	63	52	42	33	33	25	25	25	25	25	
Date	Nov.													Dec.						
	11	12	13	14	16	23	24	25	26	27	28	29	30	1	2	3	4	5	6	

In five cases serial examinations of the peripheral blood were made during the course of treatment with ACTH or cortisone. In case 9 a few "L.E. cells" were found in the pre-treatment smears. They were still present on the fourth day of treatment but none has been found in the specimens examined since that time. In case 10 many of the abnormal cells were seen before cortisone therapy; and although they definitely decreased in number during treatment, a few were found in each smear. Large numbers were again seen one month after cessation of cortisone administration. In case 11 also treated with cortisone,

the "L.E. cells" diminished in numbers but were always found in each of 16 specimens during and in the immediate post-treatment period. Case 8 was given very large doses of ACTH over a period of 29 days. Many cells were present before treatment and again, although apparently decreased in number, they were found with relative ease in all of six examinations made during the month of therapy. In Case 17 there was no significant change in the number of cells during treatment and in the week after ACTH was discontinued.

It is difficult to make quantitative studies with this technique. The observations are being continued and all that can be said at present is that in three of these five cases there seemed to be a decrease in the number of "L.E. cells" and in one none could be found on intensive study of the smears taken in the two months' period after therapy.

Serum Proteins: Determinations of serum globulin concentration were made before and during treatment in each case. The concentration before treatment was greatly increased in some patients. In all instances there was a striking fall in the gamma globulin fraction during the administration of ACTH. In several patients the non-specific complement titer was also determined and rose sharply after the start of therapy in each instance (Table 3). This inverse variation of complement titer and gamma globulin concentration has also been noted by Vaughan (2). In many cases there was also a definite rise in serum albumin concentration during treatment. Similar results were recorded in a patient treated with cortisone.

PERIARTERITIS NODOSA

A case of florid periarteritis nodosa has been under observation in the hospital since December 23, 1949 during which time he has received intermittent treatment with ACTH. The course of this patient's illness and the results of serial biopsy studies are of interest and will be reported in detail.

Goldman and his coworkers (11) have reported the immediate results following the administration of 40 mgm. of ACTH daily for 15 days to a case of periarteritis nodosa. There was marked improvement in the signs and symptoms. Stillman and Bayles (12) had similar results in two cases, one of which relapsed when therapy was discon-

tinued and the other maintained improvement for a period of ten weeks. Shick and his coworkers (13) have also reported briefly on the treatment of five cases with this disease, three of whom were given cortisone and the other two ACTH. Despite initial improvement two of the patients died from cardiac and renal failure, after 75 and 146 days, during which time they had received, respectively, 3.6 and 13.4 grams of cortisone. At post mortem study there was healing of the arterial lesions, but both had widespread visceral infarctions, apparently secondary to obliteration of the vessels during the treatment period.

CASE REPORT

P. D. (JHH 470511)

This 57 year old police detective was admitted to this hospital on December 27, 1949 because of severe asthma, diarrhea, extreme loss of weight and polyneuritis. The family history was non-contributory and he had had no serious illnesses prior to the onset of the present illness.

In April 1948, he first developed asthmatic symptoms which became increasingly severe over the following six months. Skin tests revealed no specific sensitivities and bronchoscopic examination revealed no abnormalities. In September 1948, there occurred an unusually severe and continuous attack of asthma requiring hospitalization for a period of ten weeks. Aside from asthma no other abnormalities were noted on physical examination. The temperature was normal, the sedimentation rate was 20 mm./hr. and the white cell count was 9,100 with 51% eosinophils. X-ray of the sinuses revealed some chronic infection of the frontals, ethmoids and antra. During his stay in the hospital a herniorrhaphy was performed, and before discharge at a time when the asthma was greatly improved the eosinophils were only 11% of a total of 7,350 white cells.

He continued to have mild asthma and on December 22, 1948 was readmitted to the hospital because of uncontrollable dyspnea of five days duration. He was again afebrile and showed only the signs of asthma on general examination. There was no eosinophilia. X-ray of the chest showed extensive infiltration in both lung fields. After a stormy course he improved and on January 15, 1949 a submucous resection and bilateral ethmoidectomy was performed.

He was readmitted again on April 12, 1949 for severe asthma of three days duration. The physical examination was the same. The white cell count was 19,000 but no differential was recorded. X-ray of the chest showed extensive infiltration of each lung with patches of consolidation in the left lung. He remained in the hospital for 64 days because of frequent severe attacks of asthma requiring oxygen, epinephrine-in-oil, rectal ether and other symptomatic medications for relief.

During a subsequent admission in July 1949, at which time there was no

eosinophilia, a right pulmonary plexus resection was done. He was discharged on August 22, 1949 "much improved."

However, one month later his asthma was as severe as previously and after two days of cough productive of bloody sputum he was readmitted for the fifth time. The findings were as on the previous admissions. The white cell count was 12,400 with eosinophils 1%. He slowly improved and on September 28, 1949 a left pulmonary plexus resection was performed. At each operation four grams of sulfanilamide was placed in the pleural cavity. After a stormy postoperative course he gradually improved. Microscopic examination of a mediastinal lymph node showed hyperplasia and marked eosinophilic infiltration.

About November 15, 1949 diarrhea began with some cramping but no grossly bloody stools. After two weeks he noticed soreness of the mouth and some edema of the ankles. He began to have pains in the muscles of the forearms and legs with severe numbness and tingling of the hands and feet. Some asthma was present and the patient was readmitted on December 14, at which time he was afebrile but had obviously lost a great deal of weight and appeared chronically ill. There was some emphysema and a few crepitant rales were heard at both lung bases. The legs were weak and there was tenderness to pressure over the calf muscles. The knee and ankle reflexes could not be elicited. There was some loss of cutaneous sensibility over the lower legs and feet and diminished position and vibratory sense. Similar neurological abnormalities present in the lower part of the forearms and the hands. The blood pressure was 110/70. The urine was free of albumin, but the sediment contained a few erythrocytes and white cells. The total white blood cell count was 19,000 with 20 per cent eosinophils. The red cell count was 4.15 million with 80 per cent hemoglobin. The stools were guaiac positive. The spinal fluid was normal. On December 16, 1950 biopsy of the right pectoral muscle showed extensive lesions of periarteritis nodosa and he was transferred to the Johns Hopkins Hospital for treatment with ACTH.

Examination on admission showed T. 99.4°F (rectal) P. 88; R. 24; blood pressure 110/75. He was chronically and acutely ill and had lost an enormous amount of weight. The skin was moist and loose. Axillary and inguinal lymph nodes were definitely enlarged. The chest was emphysematous in shape and expansion was minimal. Expiration was prolonged and moderate numbers of sibilant and sonorous rales were heard throughout both lung fields. The heart was normal. The liver and spleen were not enlarged. There was hyperaesthesia localized to the first two fingers of each hand extending over the palms to the base of the thumbs. There was diminished sensation over the lower legs. The deep tendon reflexes were barely obtained. There was generalized weakness but the muscles innervated by the median nerves were almost totally paralyzed.

There was a slight anemia with hemoglobin 13 gms. and hematocrit 39.0. The sedimentation rate was 31 mm./hr. The white cell count was 14,500 with an eosinophil count of 5,786 per cu. mm. The guaiac test on the stool was positive. The urine was normal. Biopsy of muscle (December 29) showed extensive lesions of periarteritis nodosa as had the first one taken two weeks earlier (Fig. 5).

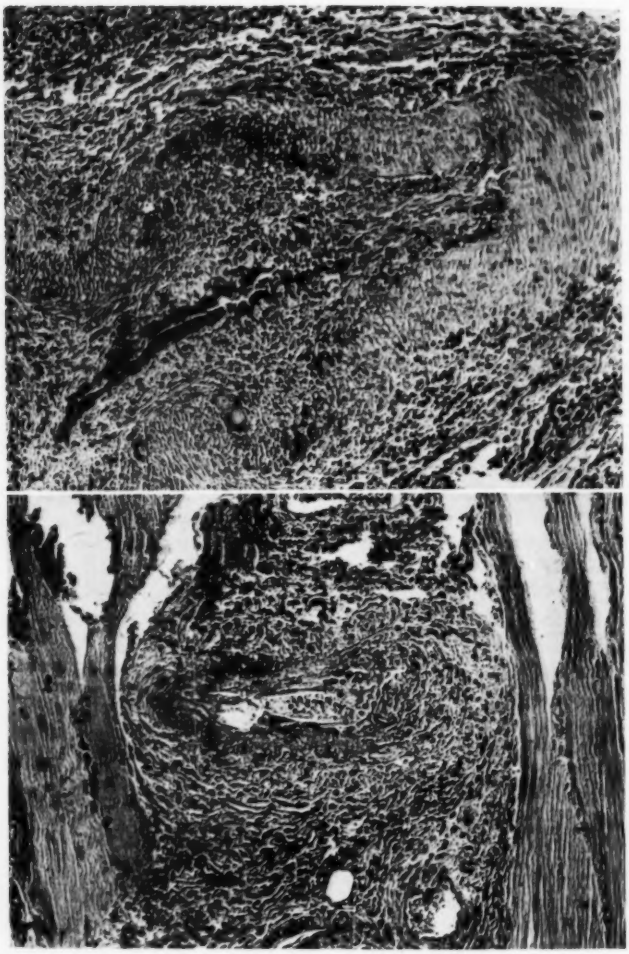

Figure 5: (S.P. 49–5154) PERIARTERITIS NODOSA BEFORE TREATMENT

Upper) An artery in muscle taken from the right pectoral region showing florid periarteritis nodosa with necrosis of the vessel wall, aneurysmal dilatation, myriads of eosinophils and beginning organization of the thrombus. There are several multinuclear giant cells, familiar in the lesion of periarteritis nodosa.

Lower) Periarteritis nodosa, (S.P. 49–5154). Section of pectoral muscle before treatment showing an artery with fibrinoid necroses of the wall and perivascular infiltration of mononuclear cells and many eosinophils.

The patient complained of severe paresthesias in the hands and feet, moderately severe asthma continued together with severe watery diarrhea. ACTH (Armour) was begun on December 31, and it was found to be necessary to give 150 mgm. a day before the eosinophil count dropped below 50 per cu. mm. He received during this first course 2868 mgm. over a period of 37 days, the dose gradually being tapered from 150 mgm. daily to 20 mgm. a day.

The asthma disappeared within a few hours and within two days the paresthesias had diminished in intensity and movement of the fingers was moderately improved. The vital capacity measured from 1.9 to 2.8 liters. His sense of smell returned and his appetite became enormous. On January 4 stools became semi-solid for the first time in six weeks, and by January 7 he no longer had diarrhea.

The biopsy was repeated on January 9 (left pectoral). Numerous small vessels were present which showed healing of the periarteritic lesions. Some had thrombosed and then recanalized (Fig. 6).

As the dose was lowered to 100 mgm. daily on January 9 his condition became static, he gained no weight although the diarrhea had subsided, and mild paresthesias persisted. The only abnormal finding resulting from the ACTH administration was a serum potassium level of 2.8 m.eq./liter. Potassium chloride was administered orally which precipitated some diarrhea. He was placed on a low residue diet and the diarrhea subsided rapidly.

On January 19 while receiving 80 mgm. daily of ACTH, he suddenly developed very severe, crampy abdominal pain. The abdomen was soft and peristaltic activity was increased. After atropine (0.4 mgm.) a considerable amount of flatus was passed and the pain subsided. During the night he experienced some abdominal soreness but had no pain although he complained of nausea. The following morning he felt quite well, the abdomen was soft without tenderness and he ate a normal breakfast. A short while later he suddenly developed an excruciating, burning pain localized to the left upper quadrant. The temperature and pulse rate were normal. The abdomen was rigid and tender with generalized rebound tenderness. It was felt that a generalized peritonitis was present and he was taken to the operating room within two hours of the onset of the acute pain. The white cell count was 27,000. When the abdomen was opened through an upper midline incision, thin cloudy fluid was encountered. Search of the stomach and duodenum revealed no perforation but on dissection around the lower duodenum a large amount of thick creamy, foul smelling pus was encountered suggesting low intestinal perforation. An incision was then made through an old hernia repair in the right lower quadrant. The appendix, however, proved to be normal and was removed. On examining the lower ileum a ruptured Meckel's deverticulum was found and repaired.

The patient withstood the 140 minute operation extremely well. During the postoperative period there was no fever or elevation of pulse rate, he experienced no pain and required no analgesics. Both operative sites healed quite normally as had the previous biopsy lesions. ACTH was continued throughout the period of postoperative convalescence. The patient was anxious to eat as soon as he had

Figure 6: PERIARTERITIS DURING TREATMENT WITH ACTH

Upper) (S.P. 50–74.) Section from pectoral muscle on tenth day of treatment. Artery in the muscle shows healed destruction of a segment of the wall with an organized, recanalized thrombus in the lumen.

Lower) (S.P. 50–240.) Section of appendix, removed on twentieth day of treatment. Artery in the wall of the appendix showing healed periarteritis nodosa with an organized thrombus in the lumen. There are hemosiderm-laden macro phages in the organized thrombus and in the fibrous tissue about the artery.

fully awakened from the anesthetic. Penicillin and dihydrostreptomycin were administered for ten days.

Microscopic sections of the appendix showed numerous small vessels which were the seat of healed lesions of periarteritis nodosa. Many of them contained organized thrombi and several had recanalized (Fig. 6).

January 27 there occurred a transient bout of urticaria which subsided within 24 hours. The daily dose of ACTH at this time was 40 mgm.

Another muscle biopsy (left pectoral) was obtained on February 1, 1950 which again showed numerous lesions in all stages of healing with no evidence of the once very active inflammatory process (Fig. 7).

At the time the first course of ACTH ended on February 6 the diarrhea had remained absent but there had been no weight gain in spite of the increased appetite and intake of food. Asthma was still quiescent but, although the paresthesias had lessened and his strength in the affected muscles was moderately improved, there was no prominent change in the peripheral neuritis.

By February 22 the asthma had returned with moderate severity and the patient began to experience pain in the thorax suggestive of an intercostal neuritis. He also developed a few erythematous subcutaneous nodules on the palms of the hands. The eosinophil count had risen to 1200 per cu. mm. on February 26. The asthma grew progressively more severe and the eosinophil count steadily rose.

March 3 he developed high fever (104) with a shaking chill and signs of lobular pneumonia appeared in both lungs with evidence of confluence in the right lower lobe in the roentgenogram. However, this episode subsided rapidly without specific treatment. Blood cultures were sterile and no pathogenic organisms were found in the sputum.

On March 7 another pectoral muscle biopsy was taken which again showed lesions, all of which were in the healing stage.

Deterioration of the general condition and severity of the asthma prompted a second course of ACTH which was begun on March 7 with an initial dose of 40 mgm. every six hours. The eosinophils fell precipitously, the general condition improved rapidly and the asthmatic symptoms vanished in less than 48 hours. The dose of ACTH was gradually tapered and discontinued on March 17, 1950. The eosinophils promptly rose to 1177. By March 22 he again had rather severe asthma and some return of his diarrhea. His condition grew steadily worse and on March 28 ACTH was resumed (12.5 mgm. every six hours). There was no improvement and on March 30 the dose was raised to 100 mgm. daily. After four days on this regimen with no improvement the dose was raised to 161 mgm. daily. On April 5 he was free again of asthma at which time the eosinophils had fallen to 297. The dose of ACTH was lowered to 120 mgm. and the following day his asthma returned and the eosinophil count rose to 889. As the dose of ACTH was gradually tapered his clinical condition grew worse. The drug was stopped on April 21, 1950. His asthma was much more severe within 24 hours. However, the biopsy (left pectoral) taken on April 13 (Fig. 7) showed no fresh lesion but only the healing seen previously.

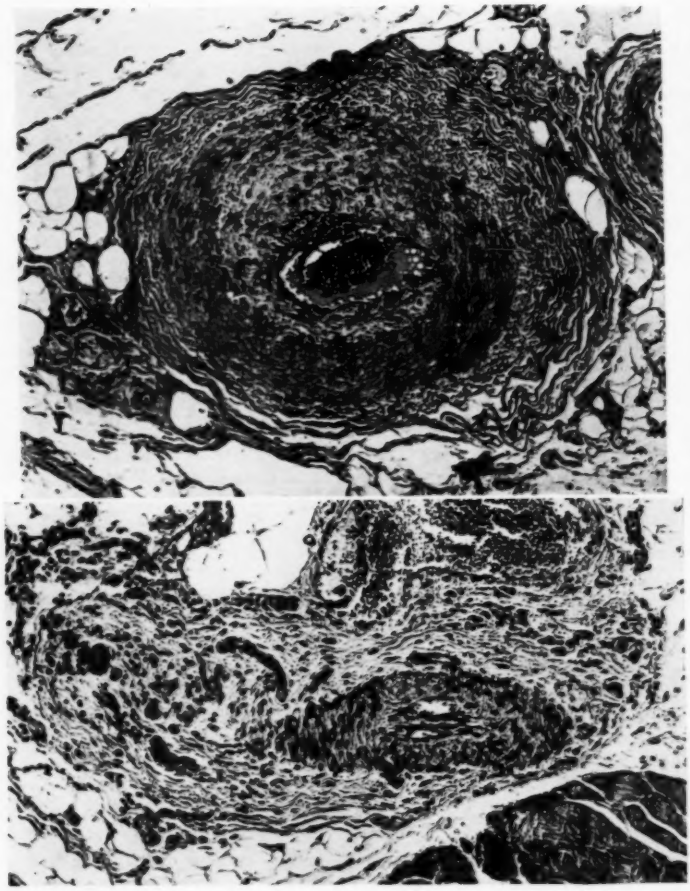

Figure 7: Periarteritis Nodosa During and After Treatment

Upper) (S.P. 50–436.) Section of pectoral muscle taken on thirty-first day of treatment. Artery in the muscle shows healed destruction of a segment of the wall and intimal fibrosis.

Lower) (S.P. 50–957.) Section of pectoral muscle taken eightieth day after start of treatment and forty-third day after last dose of ACTH. Artery in muscle shows healed destruction of part of its wall, a recanalized thrombus in the lumen, and a perivascular scar containing lymphocytes, plasma cells and hemosiderm-laden macrophages. Careful search of numerous sections revealed no fresh lesions.

During the latter part of April the patient became very depressed, threatened suicide, and continued to have severe asthma. The neuritis remained stationary and there was little diarrhea. During May he steadily grew worse with great weakness, mental depression, and constant asthma. He had delusions of persecution and was kept under suicidal observation. During this period his eosinophil count ranged from 510 to 2,080 per cu. mm.

Early in June his diarrhea gradually returned and the severity of his asthma fluctuated from day to day.

June 22 there was a dramatic increase in the severity of his peripheral neuritis with intense pain and paralysis of the hands and lower legs with inability to void. He developed numerous urticarial lesions on his thighs. The asthma and diarrhea were quite severe at this time, and on June 24 the eosinophil count was 35,000 with a total white cell count of 50,560 per cu. mm.

The following day administration of Adactar (ACTH with aluminum phosphate) was begun, 100 mgm. every 12 hours, the eosinophil count promptly fell to 9,400. Within 48 hours the asthma was under control but demerol was still required for relief of pain. The sense of well-being improved rapidly during the first three days. Adactar is being continued. On the third day of therapy the total white count was 24,200 with 10,200 eosinophils per cu. mm. The kidneys even after so long a period of active periarteritis show no evidence of impaired function and the blood pressure remains normal.

DISCUSSION

There can be no question of the efficacy of ACTH and cortisone in controlling the active manifestations of disseminated lupus erythematosus (DLE). In each case which received adequate amounts of these agents there was a prompt and dramatic improvement in the general systemic manifestations with disappearance of lassitude and asthenia, increase in appetite, defervesence, subsidence of joint manifestations and rapid improvement in other clinical features such as the pleuritic pain and cutaneous lesions. There is not yet enough evidence to evaluate with finality the influence of ACTH and cortisone on cerebral, cardiac, and renal dysfunctions but the results to date are rather discouraging. Unfortunately, due to the protean manifestations of this disease and the characteristic fluctuations in the degree of activity and localization of the lesions the diagnosis may be difficult. Acute attacks lasting for weeks or months may be followed by periods of relative freedom from symptoms, and in the recrudescences the active lesions may be confined to certain restricted areas. For example, in one attack the only clinical features may be fever and nephritis, while

in another the only manifestations may be pleurisy with effusion. It is important to emphasize that the disease may run its entire course to death without any cutaneous manifestations. Early diagnosis and treatment before cerebral, cardiac, or renal involvement occurs is of great importance.

The fact that there may be spontaneous remissions lasting for months or even years makes it more likely that ACTH and cortisone which can control the disease in its periods of intense activity may become a very practical form of treatment. Patients described in this report have had complete clinical remissions lasting many months and several have been treated during subsequent exacerbations with no diminution in the effectiveness of the therapy. Much more must be learned about the ideal treatment schedule, whether or not interim administration between relapses is desirable, and what factors may determine the rapidity of the relapse. The results thus far are very encouraging but long term follow-up and careful study of a large series of patients is necessary before any final evaluation can be made.

It is important to be certain in each patient that sufficient doses of ACTH are given to stimulate adequately the adrenal cortex or that enough cortisone is administered to produce a maximum therapeutic response. Some patients will respond satisfactorily to 40 or 50 mgm. of ACTH per day while others will require 100 mgm. or, in occasional instances, up to 150 or 200 as in the case of periarteritis nodosa reported here. Large doses of either drug may be necessary in the early phases of treatment of DLE as the adrenal sometimes appears to be already operating at a high level of activity. These patients often have an initial eosinopenia so that the eosinophil count cannot be used as a measure of the degree of adrenal stimulation produced by the administration of the drug. The change in urinary 17-ketosteroid excretion may be utilized as an index under the circumstances. Chart 2 shows the sharp rise in the urinary 17-ketosteroid excretion after ACTH administration while the eosinophil count was fluctuating at a relatively low level and was of no practical value. However, many physicians will not have available the facilities for 17-ketosteroid determinations as criteria. One cannot rely for dosage solely on the change in temperature, or subsidence of joint symptoms as these improvements may take place with doses which do not completely suppress the disease

activity and prompt relapse follows discontinuation of treatment. A number of hematological and biochemical tests have been determined serially during treatment in these patients and the one which seems most useful from the practical point of view is the sedimentation rate. In contrast to the experience of Thorn and his coworkers (2) all patients with active disseminated lupus erythematosus who had fever also had a significant elevation in the sedimentation rate. In seven patients the rate fell to normal during the course of treatment, six under ACTH and one under cortisone. In each instance the patient has had a good clinical remission lasting from three to eleven months. In the remaining four patients whose rate did not return to normal there has been either insignificant clinical response, relapse within two weeks, or incomplete subsidence of the clinical evidence of the active disease. In the one patient whose rate was normal initially there was no fever and the only abnormalities were anemia, thrombocytopenia and "L.E. cells" in the peripheral blood.

Once the diagnosis of disseminated lupus has been established the tendency may be to attribute any subsequent episodes to the variable clinical manifestations of this disease as the involvement of any given region may simulate a variety of other illnesses involving the same area. However, these patients appear to be rather susceptible to infections. The experience in Case 3 makes it necessary to watch carefully for such a complication during therapy with ACTH or cortisone. As the dose of ACTH was being lowered in this patient he suddenly had severe muscular aching followed by a chill and eight hours later a sudden rise in temperature to 104. Approximately twelve hours later the temperature fell to almost normal levels and his symptoms abated. The question arose as to whether this represented a sudden activation of the disseminated lupus associated with the lower dose or some other complication. Blood cultures revealed a hemolytic staphylococcus aureus and the infection was successfully controlled with aureomycin. It is well to point out that the clinical picture of this septicemia was rather bizarre and that the temperature fell to normal before aureomycin was begun. Case 12 developed an empyema necessitatus during the administration of cortisone and the wound after drainage failed to show the proper formation of granulation tissue as experienced by Ragan and his colleagues (14). These experiences may indicate dif-

ficulty in the localization of an infection by the body defense mechanisms when the level of adrenal activity is high.

Ragan and his coworkers noted the delayed healing of wounds in patients receiving ACTH. In a subsequent report controlled studies in rabbits were recorded in which delay in connective tissue formation was noted during cortisone administration. Observations were made also of biopsy wounds in human subjects receiving ACTH (14). After one week of treatment (100 mgm. the first day and 40 mgm. per day thereafter) the original sites were rebiopsied. Proliferation of epithelial structures was seen, but there was no granulation tissue, leucocytic infiltration, fibroblasts or proliferation of blood vessels. These observations are important and furnish a method for studying the actions of ACTH and cortisone upon tissues. It will be noted that in the patient with periarteritis nodosa reported here, scarring of the periarterial lesions is evident with organization of intramural thrombi. For practical purposes all of his biopsy wounds healed well superficially. It is of further interest that he had a perforated Merkel's diverticulum during a period when he was receiving large doses of ACTH. Two extensive abdominal incisions were made, the intestinal rupture was repaired, and the appendix removed. He was ambulatory in the first 48 hours and clinically the wound healing appeared satisfactory. Extensive peritonitis was present at the time of operation. ACTH administration was continued throughout the post-operative period. True wound healing may not have occurred with the proper formation of granulation tissue but from the practical point of view there was no breakdown of these extensive abdominal incisions during a post-operative period with early ambulation.

SUMMARY

1. Experience gained over a period of twelve months in the treatment of 12 patients suffering from disseminated lupus erythematosus with ACTH and cortisone has been described. In general, the results have been very encouraging and complete remissions lasting up to eleven months have followed a single course of treatment.

2. Five patients who had extensive cutaneous lesions without any outstanding systemic manifestations have been observed. Four were treated with ACTH and one with cortisone. In three the results have been excellent and in two no satisfactory response was obtained.

3. The clinical course of a patient with florid periarteritis nodosa who was treated with ACTH is described. Serial muscle biopsy studies showed healing of the lesions.

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THE EFFECT OF ADRENOCORTICOTROPIC HORMONE (ACTH) AND CORTISONE ON CERTAIN DISEASES OF THE EYE IN WHICH HYPERSENSITIVITY PLAYS A RÔLE

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INTRODUCTION

After the initial successes in the alleviation of certain manifestations of drug hypersensitivity, bronchial asthma, and nasal polyps by adrenocorticotropic hormone (ACTH), interest was centered on certain diseases of the eye in which hypersensitivity supposedly plays a rôle. This organ, as the nose, enables direct visual observation of the tissue changes that may take place. The studies to be reported in this communication were begun in September, 1949 and the results in five types of ocular disease will be described: 1) non-granulomatous iritis, 2) sympathetic ophthalmia, 3) tuberculous uveitis, 4) vernal conjunctivitis, and 5) the inflammatory changes associated with herpes zoster ophthalmicus. ACTH and cortisone have proven very effective in the control of these types of ocular disease.

RESULTS

Non-granulomatous iritis is characterized by the acute onset of violent pericorneal congestion, small lymphoid keratic deposits, often with a fibrinous exudate in the anterior chamber, and minimal organic changes in the iris. The attacks are usually self-limited, lasting from one or two weeks to several months. Organic damage with posterior synechiae, capsular clouding of the lens, and atrophy of the iris occur in most instances only after repeated attacks, the eye as a rule clearing with no residual effects. There is a definite tendency to repeated attacks, and this type of iritis is usually associated with rheumatoid arthritis or follows some infectious process. It is believed to be an allergic reaction in the eye dependent upon a bacterial hypersensitivity (1).

Case 1. G. B. (JHH 511441)

A 37 year old white man complaining of iritis in the right eye was first seen by Dr. William G. Marr on August 19, 1949. The family history was non-contributory. He had been overweight for a number of years. Six years previously he had had an attack of iritis in the right eye, and since then he has had five similar attacks, usually coming on in July or August. The left eye occasionally showed a little redness or congestion but was "white" within 24 or 36 hours.

His present illness began in his right eye about two weeks previously and was characterized by marked photophobia, lacrimation, pericorneal congestion, dilated vessels in the iris, some fibrin in the anterior chamber and a positive aqueous ray. The left eye was entirely normal except for slight photophobia. The best vision in the right eye was 20/40 and in the left eye 20/15. Coincident with the eye symptoms the patient had noted the onset of soreness and stiffness of the left fifth finger which persisted.

He was admitted to the hospital where the general physical examination was entirely normal except for minimal arthritis involving the left fifth finger. This was believed to be early rheumatoid arthritis. The patient was markedly overweight. The electrocardiogram was essentially normal. There was no evidence of granulomatous disease. Serological tests for syphilis were negative, x-ray examination of the chest was normal, and there was no significant sensitivity of the skin to tuberculin. No infection was found in the nose, throat, teeth, or genito-urinary tract.

He did not improve while under treatment with pyribenzamine, local heat, diathermy and finally injections of typhoid vaccine intravenously. By the fifth of September vision in the right eye had decreased to 20/70, the inflammatory reaction had increased, there was a large amount of fibrin in the anterior chamber and the aqueous ray was reported as 4+. On September 8, 1949, he was transferred to the Medical Service for treatment with ACTH, which was started on September 11. The initial dose was 23 mgm. of ACTH (Armour Standard) every six hours, or 92 mgm. per day. The total daily dose of ACTH and the degree of clinical response are shown in Chart 1. By September 12, the eye showed a tremendous improvement, the aqueous ray was 1+, the pupil was fully dilated, which could not be achieved previously, the iris appeared free of hyperemia, the tension was normal and vision had risen to 20/30. This improvement was maintained throughout the remainder of his hospital stay.

In the last note by Dr. Frank Walsh, September 23, he stated that the eye was entirely quiet, aqueous ray was negative and there was no sign of any inflammatory reaction.

The eosinophil count dropped from 110 per cu. mm. to 11 four hours after the first dose of ACTH and remained below 50 during the entire period of therapy. The 24 hour excretion of 17-ketosteroids was 3.71 mgm. on September 9 before ACTH; 11.50 mgm. on the third day of ACTH administration and 16.05 mgm. the day after the drug was discontinued.

The patient was readmitted on May 2, 1950 because of a recurrence of the iritis

of eight days duration. He had developed an acute tonsillitis at the same time that his eye lesion recurred.

Examination revealed marked photophobia and pericorneal injection. The aqueous ray was 3+ and there was considerable fibrin in the anterior chamber. The iris was thickened and edematous with dilated capillaries. The left eye was normal. General physical examination revealed only a subsiding tonsillitis.

Cortisone acetate (Merck) was administered parenterally from May 5 to May 11 in the following daily doses: 300, 200, 100, 100, 200, 200 and 100 mgm.

In contrast to the very rapid improvement with ACTH the condition of the eye did not change until May 9, at which time the photophobia was less, the

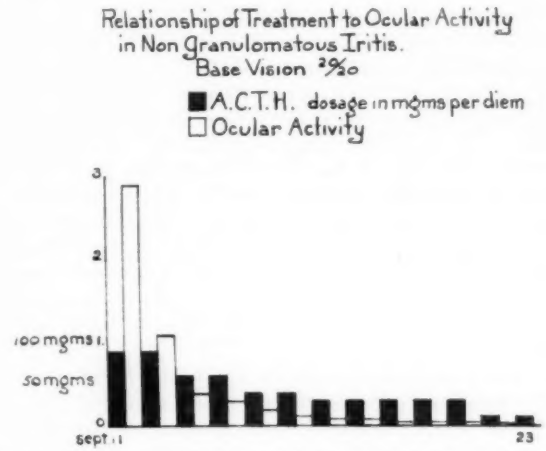

CHART 1. Case G. B. (JHH 511441) Non-granulomatous iritis. This chart shows graphically the relation between the improvement in the ocular disease and the administration of ACTH (Armour).

cornea was clearer, the stroma of the iris was less swollen, but the pericorneal injection was unchanged. Improvement was very rapid after this time and progressed more rapidly when cortisone was applied locally (one drop every hour when awake) beginning on May 11. The local treatment was continued until May 15. He was discharged on May 16 at which time the eye was white, the vision was 20/20, and only a few pigment deposits remained on the anterior surface of the lens.

Summary: This 37 year old white male had a typical non-granulomatous iritis and minimal evidence of rheumatoid arthritis. The inflammatory reaction in the eye cleared rapidly following the administration

of ACTH and vision improved. Eight months later he had a recurrence of the iritis which again was treated successfully with cortisone administered parenterally and locally although the improvement was less rapid.

Case 2. G. C. (JHH 534114)

This 52 year old white woman was first examined on March 29, 1950. The family history was non-contributory. In 1932 she had an attack of rheumatoid arthritis affecting both knees and at the same time developed hay fever. Since that time she had had repeated attacks of arthritis involving at one time or another almost all of the joints with some residual deformity of her fingers.

The present illness began in September, 1949 when she had the first of repeated attacks of iritis in both eyes. She was treated with antibiotics, vaccines and various forms of non-specific protein therapy. Some infection was found in her maxillary sinuses which were lavaged on repeated occasions. She had taken pyribenzamine for the previous six months without benefit. Four infected teeth had been removed. Her vision had declined from an initial level of 20/40 to 20/200 in each eye.

When she was first seen her eyes were normal on external examination. Opthalmoscopic examination showed a blurred reflex in both maculae, evidently due to retinal edema. No exudates were visible. One small petechial hemorrhage was present in the right fundus. Slit lamp examination was entirely negative. The visual fields were normal in outline but showed a large paracentral scotoma in each eye. The diagnosis was recurrent non-granulomatous uveitis with bilateral macular edema.

She was admitted to the hospital on April 9, 1950 for cortisone therapy. At that time the maximum vision in the right eye was 20/70 and in the left eye 20/70. Cortisone was begun on April 12. She received 300 mgm. the first day; 200 mgm. the second and third days; and 100 mgm. per day thereafter for a period of six days, making a total dosage of 1300 mgm. of cortisone given parenterally. There was a steady subsidence of retinal edema and when the patient was discharged on April 22, 1950 the corrected vision in the right eye was 20/30+ and in the left eye 20/30. The retinal edema entirely disappeared, and there was a good macular reflex on both sides with a little superficial macular degeneration remaining. The central vision was slightly spotty but no actual scotoma could be plotted, there apparently being a number of very small paracentral scotomata instead of the large solid scotoma present on admission.

Summary: This 52 year old white female suffered from rheumatoid arthritis and had had repeated attacks of non-granulomatous iritis involving both eyes. At the time of treatment with cortisone given parenterally she had extensive retinal edema with a large paracentral scotoma in each eye. There was complete disappearance of the edema

under cortisone. The vision improved, and no definite scotomata could be demonstrated.

Sympathetic Ophthalmia

This disease is a specific bilateral uveitis of unknown etiology with a characteristic clinical and pathological picture. It follows a penetrating wound (trauma or operation) which involves the uveal tract and the injured eye is known as the exciting eye. After a varying interval of time, usually two to twelve weeks but occasionally as long as several years, a uveitis develops in the second, or sympathizing eye. After this event has taken place the clinical course is identical in the two eyes. It is characterized by an insidious onset and a protracted course, with marked organic changes in the eyes, the formation of posterior synechiae, capsular clouding of the lens, and secondary glaucoma which may be followed by phthisis. The disease usually runs its course in six to twelve months with most cases resulting in blindness although a few recover with impaired vision. The histological picture consists of epitheloid and lymphoid cell infiltration of the uveal tract with phagocytosis of the pigment by epitheloid and mononuclear cells. It has been demonstrated that in the early stages of the disease there is almost invariably a hypersensitivity of the skin to the organ-specific pigment of the uveal tract. When this pigment is injected intracutaneously the histological picture is identical with that in the involved eye (2)

Case 3. S. L. (JHH 523497)

A 66 year old white female was admitted on December 12, 1949 with a diagnosis of sympathetic opthalmia, the right eye being the exciting eye and the left the sympathizing eye.

The family history and past history were non-contributory. The right eye had been the site of an uneventful cataract operation on October 23, 1949.

The present illness began on December 4, with a low grade ciliary congestion and small keratic deposits in the left eye. The patient developed a sensitivity to atropine on December 15. Atropine was discontinued and evidences of the hypersensitive reaction disappeared by December 17.

On admission, physical examination showed evidences of mild arteriosclerotic heart disease. A faint trace of reducing substance was present in the urine, with a fasting blood glucose of 108 mgm. per cent. There was no evidence of granulomatous disease, the serological tests for syphilis were negative, and radiographic studies of

the chest were normal. There was a negative skin test to 0.1 mgm. tuberculin, a normal pattern of serum protein, and all serological and cutaneous tests for Brucellosis were negative.

Examination of the eyes on December 17 revealed the following: *Right eye:* Slight pericorneal congestion. The pupil was widely dilated, peaked above at twelve o'clock. There was no visible evidence of iris prolapse. The tension was normal. On ophthalmoscopic examination the vitreous was so cloudy that only an occasional vessel could be seen. Slit lamp examination showed edema and thickening of the iris, some feathery exudate on the hyaloid face of the vitreous, suggesting

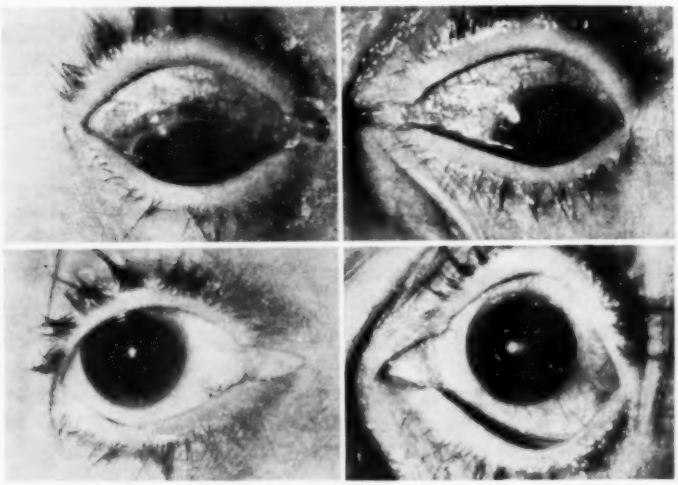

FIG. 1. S. L. (JHH 523497) Sympathetic ophthalmia. Treatment with ACTH. a) Upper left. Right eye before treatment. b) Upper right. Left eye before treatment. c) Lower left. Right eye three days after beginning ACTH therapy. d) Lower right. Left eye, same date as in (c).

sympathetic infiltrated tissue breaking through the pigment edge of the iris. There was one small Koeppe nodule. There were no keratic deposits. The aqueous flare was 2+. Vision, corrected, was 4/100 (Fig. 1a). *Left eye:* There was low-grade pericorneal congestion, irregularity of the pupil with obvious posterior synechiae, and manifest nuclear clouding of the lens. Ophthalmoscopic examination showed a blurred red reflex peripherally. No fundus details could be seen. Slit lamp examination showed definite, fairly large keratic deposits with some greasy exudate on the posterior surface of the cornea. The iris was thickened and edematous, and between 7 and 8 o'clock there was some inflammatory tissue spreading from the pupillary edge over the anterior capsule of the lens. The aqueous flare was 1+

and vision was 2/100 corrected. The clinical diagnosis was early sympathetic ophthalmia (Fig. 1b).

ACTH (Searle) was started December 16, 1949 at 6 p.m. The dosage was 240 mgm. per day (60 mgm. every 6 hours). On December 19, there was a definite objective improvement in each eye, the inflammatory reaction having largely disappeared. The pericorneal inflammation had subsided in both eyes, the media in the right eye was much clearer and fundus details could be faintly seen. The Koeppe nodule on the right pupillary edge had been absorbed. Vision had risen to right 10/100 and left 4/100 (Fig. 1c, d).

On December 20, treatment with ACTH (Armour) was begun, the dose being 60 mgm. (Armour Standard) per day; reduced on December 21 to 50 mgm.; on December 22 to 40 mgm.; on December 25 to 30 mgm.; on December 26 to 20 mgm.; and on December 28 to 10 mgm. per day. During this time the eyes continued to improve steadily. All evidences of inflammation subsided. The media became clearer. The right fundus could be well visualized and showed a peculiar yellowish edema around the nerve and some generalized retinal edema involving the mid-zone and peripheral fundus. The left fundus could not be seen on account of the lenticular opacity. The aqueous flare in both eyes became negative. There were no perceptible changes in the thickened irides. Corrected vision rose to right 20/50 and left 30/200.

There was a definite recurrence of the inflammatory phase in the eyes shortly after the ACTH was cut to 10 mgm. per day. This began on December 31, with a recurrence of the pericorneal congestion, an increase in the aqueous flare with cells and the appearance of fibrin in the anterior chamber of the right eye. There was a reduction of vision to 20/70 in the right eye and 20/200 in the left eye.

On December 31, the ACTH was increased to 20 mgm (Armour Standard) per day. Within two days there was again a decided improvement in the inflammatory picture, the vision rising to 20/50 in the right eye with a subsidence of the pericorneal congestion, absorption of the fibrin and clearing of the vitreous.

There was little change in the ocular picture up to January 9, the vision remaining in *status quo*, when the ACTH was increased to 50 mgm. per day. This was followed by a further improvement in the left eye, the keratic precipitates absorbing and the vision rising to 20/40. The aqueous flare, however, remained at 1+.

On January 12, there was an increase in the eosinophils, and the dose of ACTH was increased to 100 mgm. per day. On January 14, this was followed by complete clearing of all external inflammation. ACTH was then discontinued. There was an increase in the vitreous clouding and, on January 16, right vision declined to 20/100. Beginning on January 20, however, there was again a clearing of the vitreous, and on January 22, vision had risen to 20/50 and all inflammatory signs again began to subside. On January 27, there was a slight relapse. ACTH was readministered on February 1, the dose on the first day being 100 mgm. There was again an immediate improvement, and after the first day's treatment the amount of ACTH given was gradually reduced, and finally was permanently

discontinued on February 8. The eyes thereafter remained relatively unchanged, with minimal evidences of inflammation. On February 20, right vision was 20/70 + 2 and left vision 20/200. There was still a trace of pericorneal hyperemia, and a faintly positive aqueous flare in each eye. However, all inflammatory debris had largely disappeared from the posterior surface of the corneas, and in the left eye the keratic precipitates were much smaller. The patient was discharged on February 22, 1950. A satisfactory eosinophil response was maintained throughout the treatment period.

On March 12, 1950, the patient was reexamined. Right vision was then 20/40 and left vision 20/200. The right eye continued to show a few cells in the aqueous, a moderate haze in the vitreous, and a 1+ aqueous flare. There were no keratic deposits. The left eye showed numerous fine keratic deposits, the organic changes in the iris were more marked, the pupil was smaller and posterior synechiae had formed. The tension in both eyes appeared normal.

It takes ten to fourteen days for the usual pigment skin test to show the characteristic tissue reaction. Two tests (2) were done on this patient. In one the antigen was injected intracutaneously one week before ACTH therapy and the second at the time therapy was begun. Both tests were negative.

Summary: This patient with sympathetic ophthalmia had under ACTH administration an immediate clearing of the inflammatory phases of the disease. One short relapse while under treatment was again controlled when the dosage of ACTH was increased. The drug was again discontinued for four days with a slight recurrence of symptoms. After eight days further treatment, the ACTH was discontinued, this time without significant relapse. At the termination of treatment there remained only minimal signs of an inflammatory reaction, but the evidences of organic change in the eye were unaltered. The last followup report in May, 1950, has revealed no recurrence of the sympathetic disease.

Case 4. E. M. (JHH 525991)

A 62 year old white female was admitted on January 13, 1950, with a diagnosis of sympathetic ophthalmia, the right eye being the exciting eye and the left the sympathizing eye.

The family history and past medical history were non-contributory. The present illness began about December 7, 1949, when the patient developed an acute glaucoma in the right eye. On December 16, an operation (iridencleisis) on the right eye was performed at another hospital. There was a history of an uneventful post-operative course, but about January 8, the vision in the left eye became blurred and the eye inflamed. A diagnosis of sympathetic ophthalmia was made and the patient was referred for ACTH therapy.

On admission, the general physical examination was essentially normal except for a cloudy left antrum. There were no evidences of systemic granulomatous disease, syphilis, sarcoidosis, brucellosis, or tuberculosis on examination or by laboratory tests.

Examination of the eyes on January 13, 1950 was as follows: *Right eye:* There was marked pericorneal congestion, a shallow anterior chamber with striate keratitis, a blurred red reflex, and no fundus details could be seen. Tension was extremely low. Slit lamp examination showed folds in Descemet's membrane, no keratic deposits, and a positive aqueous flare. Vision was reduced to counting

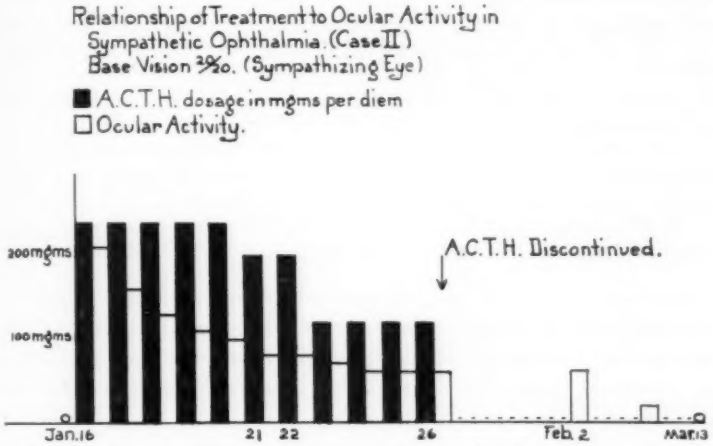

CHART 2. E. M. (JHH 525991) Sympathetic ophthalmia. Treatment with ACTH. This chart shows the total daily dose of ACTH (Searle) and the degree of clinical improvement.

fingers at one foot. *Left eye:* There was moderate pericorneal congestion, marked thickening and edema of the iris, and a large posterior synechia at nine o'clock. Tension was normal. Ophthalmoscopic examination showed a moderate vitreous haze and an essentially normal fundus. Slit lamp examination showed a normal cornea, no keratic deposits, a greatly thickened iris with one suggestive deep nodule, posterior synechiae and a positive aqueous flare. Vision corrected was 20/50.

A diagnosis of sympathetic ophthalmia was made, and ACTH was started on January 16, 240 mgm. per day (Searle) (60 mgm. every 6 hours) being given initially. On January 21, the dosage was cut to 200 mgm. per day, on January 23, to 120 mgm. per day, and ACTH was discontinued on January 26, after ten days treatment, a total of 3940 mgm. having been given. The total daily dose of ACTH and the degree of clinical improvement are shown in Chart 2.

There was improvement noted in the eyes after 24 hours of treatment. The pericorneal congestion subsided, the striate keratitis lessened and the vitreous cleared. By January 20, the vision had risen to right 5/200, and left 30/30. There was little change in the organic thickening of the right iris, the pupillary margin being adherent to the anterior capsule of the lens. The left iris improved, the synechiae were freed and the pupil became round and regular. There was, however, an increase in the keratic deposits. On January 26, the keratic deposits on both corneas were more marked, but the aqueous flare was weakening. On February 2, one week after cessation of the ACTH, the eyes were practically free of inflammation, the keratic precipitates were much smaller, and the aqueous flare faintly positive in the right eye and negative in the left eye. On February 6, right vision was 5/200 and left vision 20/40 corrected. The right eye showed a trace of residual inflammation while the left was entirely inactive (Chart 2). The patient was discharged. A satisfactory eosinophil response was maintained throughout the treatment period.

The patient was thereafter followed in the Out-Patient Dispensary. There was continued improvement. On March 13, right vision was 8/200 and left vision was 20/20 (−1). Both eyes were white and free of any evidences of inflammation. The keratic precipitates had disappeared almost completely. There had been no recurrence at the time of the last visit on June 10, 1950.

Summary: A definite case of sympathetic ophthalmia, treated for ten days with fairly large doses of ACTH. Improvement was noted 24 hours after institution of therapy and was steadily maintained during treatment and after treatment was stopped. There was at first an increase in the organic changes, but this subsided leaving only keratic deposits. At the end of two months the eyes appeared entirely quiescent, with 8/200 vision remaining in the right exciting eye which had been the site of an acute glaucoma, and normal vision resulting in the left sympathizing eye.

A third case which was in an advanced stage and very severe was treated fourteen weeks after onset with local instillation of cortisone. The exciting eye (left) which had been the seat of a cataract operation was in phthisis with questionable light perception. Both eyes were markedly inflamed with ciliary tenderness and pain. The right eye showed advanced capsular clouding of the lens with extensive posterior corneal opacities. Large keratic deposits were present and a strongly positive aqueous flare. Ciliary tenderness and pain were gone after 48 hours and the ciliary congestion was much less. After ten days the eyes were completely free of all external evidence of inflammation.

The aqueous flare was still positive but the greasy deposits on the posterior corneal surfaces had been absorbed. Vision did not improve.

Tuberculous Uveitis

This is a typical granulomatous inflammation characterized by an insidious onset with low-grade ciliary congestion, large greasy keratic deposits, organic thickening of the iris and often visible tubercles. The course is usually protracted with exacerbations and remissions. Organic changes in the eye with posterior synechiae, capsular clouding of the lens, and secondary glaucoma may occur early. In the patient in whom the ocular tissues become hypersensitive as a result of the infection there is an acute inflammatory reaction dependent upon this underlying tissue hypersensitivity to tuberculin. The actual disease, however, results from an invasion of the ocular tissues by the mycobacterium tuberculosis, and treatment with dihydrostreptomycin and promizole is indicated (3).

Case 5. A. F. (JHH 262058)

A 29 year old colored woman was admitted on April 25, 1950 for treatment of an acute tuberculous uveitis. The family and past histories were non-contributory.

Nine years previously she developed a parotid swelling which on biopsy showed sarcoidosis. During the following year she developed a generalized lymphadenopathy. X-ray examination of the chest revealed hilar adenopathy. Repeated examinations of sputum and gastric washings were negative for tubercle bacilli both on smear and culture, but the tuberculin test was strongly positive leaving an ulcerated area which took several months to heal. The total serum protein was 8 gms. per 100 cc. with 4 gms. of globulin. Over a period of several months the lymph nodes and the parotid gland decreased progressively in size. She remained well until two years before admission when she developed fever and axillary lymphadenopathy. Biopsy revealed a caseous gland and a diagnosis of tuberculosis was made. One year before admission a transient infiltration appeared in the right lower lung field and she developed a severe iritis in the left eye with secondary glaucoma. Two months before entry the pulmonary lesion reappeared following which she developed a severe acute iritis on the right.

Physical examination revealed no elevation in temperature. There was a generalized lymph node enlargment and a large soft, non-tender swelling at the angle of the jaw on the left side. The right eye showed marked pericorneal injection, heavy mutton-fat keratic deposits, a positive aqueous ray with a thickened edema-

tous iris without nodule formation (Fig. 2). There were heavy clouds in the vitreous. The tension varied from 19 to 40 mms. Vision was limited to hand movements.

ACTH was begun on May 11, 1950. The initial dose was 25 mgm. (Armour Standard) every six hours. The eosinophil count fell promptly from 110 to 0. Within eight hours the eye was free of pain and the pericorneal injection was greatly reduced. After six days of treatment all ciliary congestion had faded, and the aqueous ray was negative (Fig. 2). Tension remained elevated for ten days and then fell to normal. Vision increased to 20/100 and there was considerable clearing in the vitreous. The dosage of ACTH was gradually reduced to 40 mgm. per day on May 23. On May 25, coincident with a rise in the eosinophil count from 0 to 77, there was a reappearance of the inflammatory reaction in the eye associated with pain. ACTH was increased to 60 mgm. daily and the eye abnormalities cleared promptly. The dose was again lowered to 40 mgm. on May 31

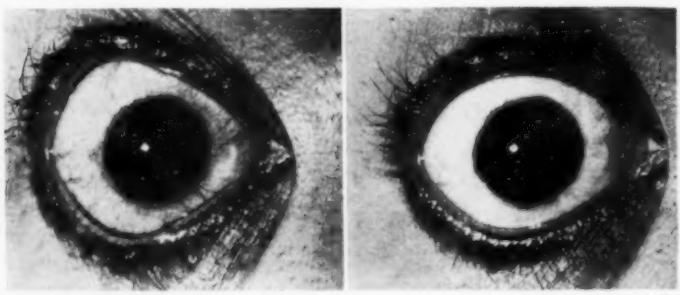

FIG. 2. A. F. (JHH 262058) Tuberculous uveitis. Treatment with ACTH (Armour). The photograph on the left is of the right eye before treatment and on the right the same eye, sixth day of treatment.

which was again followed by a relapse on June 4. The same course of events followed a subsequent reduction in dosage. On June 10, ACTH was discontinued and cortisone was applied locally to the eye (1 drop every hour when awake). There was progressive improvement and by June 13 all evidence of activity had subsided. During the entire period of hospitalization the patient was receiving dihydro-streptomycin and promizole therapy.

Summary: This 29 year old colored woman with what was diagnosed as a typical acute tuberculous uveitis was treated with ACTH. Within eight hours the eye was free of pain and the pericorneal injection greatly reduced. On the sixth day of treatment the eye was free of inflammation and vision had greatly improved. On two occasions when the daily dose of ACTH was reduced to 40 mgm. daily signs of

active inflammation returned. During a period of several weeks improvement was maintained by the local application of cortisone drops.

Case 6. J. W. (JHH 532752)

This 40 year old white female entered the hospital on March 24, 1950 because of severe tuberculous uveitis and a cutaneous reaction to atropine. The family and past histories revealed no relevant information.

The present illness began in July, 1949, when she developed an acute iritis in the left eye which subsided after several weeks under local treatment. There was a recurrence in October, 1949, and activity persisted after that time with

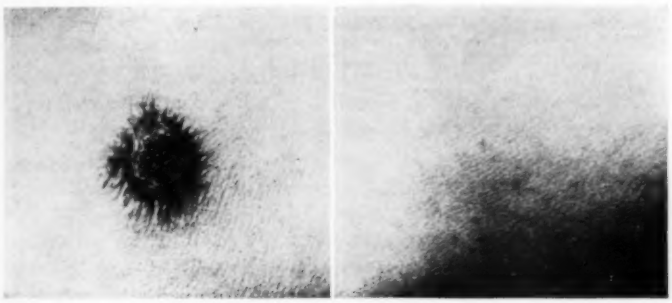

FIG. 3. J. W. (JHH 532752) Tuberculous uveitis. Intradermal reaction to tuberculin (0.001 mgm. O.T.). Left: Before treatment with ACTH (Armour). Note the large area of necrosis with sloughing. Right: Eighth day of ACTH administration. There was only a mild erythema which faded within 24 hours.

periods of increased ocular tension. Because of the increased severity of the iritis and the severe reaction to atropine she was admitted for therapy with ACTH.

Although the eye was difficult to examine at the time of entry due to the violent atropine reaction involving the lids, it was apparent that there was a severe pericorneal congestion, marked edema of the corneal epithelium, an infiltrate in the cornea, and posterior synechiae. Vision was limited to light perception. The right eye was normal. General physical examination revealed no significant abnormalities.

X-ray examination revealed a chronic pansinusitis. Intracutaneous test with tuberculin showed a very severe reaction to 0.001 mgm. with necrosis and sloughing (Fig. 3, left). Patch test to atropine also gave a marked reaction characterized by erythema and edema, with oozing and crusting of the skin.

ACTH (Armour) was begun on March 27. She received 100 mgm. for three days; 160 mgm. for three days; 120 mgm. for three days; 80 mgm. for two days; and 40 mgm. for three days. The total dose of 1420 mgm. was undoubtedly greatly

in excess of the amount needed to control the inflammatory reaction in the eye but was thought advisable because of the skin tests done during therapy to agents to which she was hypersensitive. There was a prompt and maintained eosinopenia following exhibition of the ACTH.

Within 36 hours after beginning the hormone the pericorneal congestion faded, the corneal edema cleared, and the tension became stabilized at normal levels. Slit lamp examination was now possible, as the edema of the lids had subsided, and showed some pigmented keratic deposits, one large fuzzy corneal infiltrate, some organized exudate on the anterior capsule of the lens, and a faintly positive aqueous flare. In the upper sclera near the equator a patch of subsiding deep scleritis could now be seen. The improvement continued steadily, and by the time of discharge on April 12, 1950 the eye was entirely free of inflammation. The corneal infiltrate was circumscribed, and the aqueous flare was negative. Vision had risen to 20/100.

On April 4, the patient was again challenged with tuberculin. Whereas she previously had a strong reaction to 0.001 mgm. with necrosis and sloughing, she was now completely negative to this concentration (Fig. 3, right).

Summary: This 40 year old female had a tuberculous uveitis and developed a hypersensitivity to locally applied atropine. The tuberculin reaction in the skin was strongly positive. Under treatment with ACTH the inflammatory reaction in the eye subsided completely with improvement in vision. During the administration of ACTH the intracutaneous reaction to tuberculin was almost completely blocked.

Case 7. W. B. (JHH 533134)

This 17 year old white male was admitted on March 29, 1950 with a complaint of uveitis in the left eye. The family history and past history were non-contributory. The present illness began about December 18, 1949 with inflammation of the left eye and blurring of vision. A diagnosis of tuberculous uveitis was made and the patient given repeated intravenous injections of typhoid vaccine without effect on the lesion.

On admission the right eye was normal on objective examination, but vision was reduced to 20/40 from an old amblyopia exanopsia. The vision in the left eye was 3/200. There was pericorneal congestion, haziness of the cornea, and an elevated ocular tension measuring 48 mms. on the tonometer. There were heavy mutton-fat keratic deposits and some thickening of the iris with blurring of the normal pattern. There were heavy veils throughout the vitreous, whitish reflex in the upper fundus but no fundus details were visible. The medical survey showed radiographic evidence of an old primary tuberculous pulmonary complex and a moderate hypersensitivity to tuberculin. All other examinations were normal. It

was believed the original diagnosis of tuberculous uveitis with secondary glaucoma was correct.

Cortisone therapy was begun April 4 with a dosage of 300 mgm. On the second and third days of treatment 200 mgm. were given; from the fifth to the ninth day 100 mgm., and thereafter the dose was gradually decreased and all therapy was discontinued on April 14. The total dosage was 1400 mgm. over a ten day period.

After two days of treatment clearing of the vitreous was noticed and the retinal edema was definitely less. A large exudate could now be seen in the upper fundus and there was some degeneration in the fovea below. By April 10 the outlines of the disc could be made out, and the exudate above appeared more circumscribed. The tension had fallen to 20 mms. On April 14, vision had risen to 15/200 and the retinal edema had subsided to such an extent that fundus details could be faintly seen. Tension remained within normal limits. The patient was then discharged under the care of his home physician for streptomycin and promizole therapy.

He was seen again on June 2, 1950, at the end of his course of antibiotic therapy. There was no residual evidence of active inflammation and the patient is being followed to control any secondary glaucoma.

Summary: This 17 year old schoolboy with tuberculous uveitis received a total of 1400 mgm. of cortisone over a period of ten days. There was subsidence of the retinal edema, return of tension to normal and improvement in vision from 3/200 to 15/200.

Two other cases have been treated and will be mentioned only briefly. The first, a 21 year old girl (JHH 534258) with an old healed tuberculous chorioretinitis developed an acute uveitis in the other eye. The vision was reduced to 20/50. She was placed on dihydrostreptomycin and promizole, but the vitreous continued to cloud and secondary glaucoma developed. Cortisone was first given intramuscularly and over a period of eleven days the eyes improved. When this treatment was stopped the inflammation quickly reappeared and the tension rose. With the local instillation of cortisone for eight days the external inflammation subsided and the tension returned to normal, but the vitreous remained cloudy. During the fourth week the vitreous began to clear probably as a result of the antibiotic therapy.

The second patient, a 50 year old woman (JHH 148260) had a chronic tuberculous sclero-keratitis which had responded well to antibiotic therapy, but a low-grade scleritis with edema of the lids remained. Cortisone diluted 1:3 with physiological saline solution was applied locally with a marked improvement in the inflammatory reaction and subsidence of the edema of the lid.

Vernal Conjunctivitis

This is a rather rare form of chronic inflammation which produces characteristic changes in the conjunctiva. The papillae are hypertrophied and over the whole lies a delicate bluish-white film. The evidence suggesting an allergic etiology consists in its clinical course, its seasonal recurrence in the summer months, the itching, the eosinophils in the secretion and the lack of any consistent bacterial invader. There is some evidence that patients with vernal catarrh have a higher incidence of associated allergic manifestations than do normal individuals.

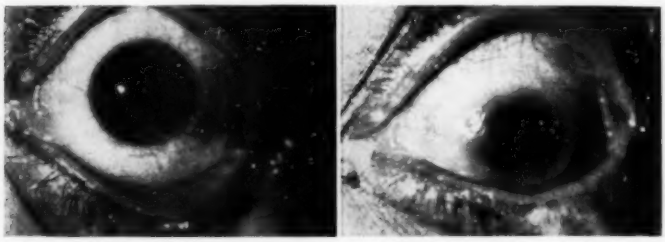

FIG. 4. A. C. (JHH 536264) Vernal conjunctivitis. Treatment with cortisone (parenterally and locally). Right: Left eye before treatment. Left: Left eye eight days after local treatment with cortisone drops.

Case 8. A. C. (JHH 536264)

An 18 year old Negro developed a bilateral conjunctivitis in April, 1944, which was characterized by the formation of huge follicles in the palpebral conjunctiva with vascularization and infiltration of the cornea. There was some improvement during the next few months, but in November, 1949, there was an exacerbation which continued until the time of admission in May, 1950. Careful study in another hospital, including biopsy, animal inoculations, and cultures had revealed no etiological factor.

At the time of admission the corneae were completely opaque and heavily vascularized (Fig. 4, right). Examination of the palpebral conjunctivae showed massive follicular hypertrophy. There were many eosinophils in the conjunctival discharge. Biopsy of a follicle showed lymphoid hyperplasia with a surrounding zone of eosinophils, the characteristic picture of vernal catarrh.

After three days of parenteral cortisone therapy (total dose 700 mgm.) there was a significant drop in the blood eosinophil count but no objective improvement was noted. At that time the local instillation of cortisone was begun (one drop every

hour when awake). During the next twelve hours there was considerable objective change and within eight days the corneae had cleared to such an extent that the irides could be easily visualized (Fig. 4, left). The follicles rapidly diminished in size. Vision rose from hand movements to 20/100. The local cortisone therapy was continued for two weeks, at which time vision was 20/40.

Summary: This 18 year old colored boy had severe bilateral vernal conjunctivitis characterized by the formation of huge follicles in the palpebral conjunctiva with vascularization and infiltration of the cornea. During the local instillation of cortisone drops the follicles diminished in size, the corneae cleared so that the irides could be clearly visualized, and vision rose from 20/100 to 20/40.

Herpes zoster ophthalmicus in some instances is characterized by multiple eye involvements which include deep keratitis, iritis, iridocyclitis and scleritis. In many severe cases the end result is blindness or greatly reduced vision. The Gasserian ganglion shows lymphocytic infiltration. Treatment has been unsatisfactory until recently, when fairly good results have been obtained with aureomycin and chloromycetin. Herpes-convalescent serum and diphtheria antitoxin may have some value if given early.

In two cases of herpes zoster ophthalmicus, associated with an anterior uveitis, local instillation of cortisone (1 drop every hour) has produced dramatic improvement in the inflammatory signs.

P. P., a 53 year old man complained of redness, photophobia and poor vision in the left eye for two months consequent to herpes zoster. He had had periods of secondary glaucoma. Cortisone drops produced an immediate sensation of improvement. The circumcorneal injection of the eye disappeared; the posterior corneal precipitates were unchanged. After six days' treatment the drops were discontinued. In two weeks the evidences of anterior uveitis returned and again responded to cortisone therapy.

Dr. W. K. M., a 60 year old white male, had right sided herpes zoster ophthalmicus with involvement of the eye. He had received chloromycetin and aureomycin over a period of two weeks prior to our examinations. There was pronounced circumcorneal injection, there were discreet patches of superficial and deep corneal involvement and numerous keratitic precipitates. The pupil was moderately dilated. The aqueous ray was 2+. Large folds were seen in Descemet's membrane. Cortisone was instilled hourly for thirty-six hours and aureomycin was continued. At the end of this period, the eye was white. Cortisone was continued for a week and the visual acuity improved from 20/200 to 20/50. Cortisone instillations were

discontinued and the eye continued to improve for three weeks, when there was a recurrence of the circumcorneal redness and reappearance of ridging of Decesmet's membrane. Further instillations of cortisone cleared the external inflammation in one day.

Summary: In two cases of herpes zoster ophthalmicus, the anterior uveitis showed remarkable improvement within a day after the local application of cortisone. When treatment was discontinued there was a recurrence of the inflammatory reaction which again responded promptly to resumption of treatment.

DISCUSSION

Just as in the case of allergic manifestations involving the mucous membranes of the nasopharynx, the effect of ACTH and cortisone on certain ocular diseases, in which hypersensitivity is considered to play a rôle has resulted in clear-cut and directly observable changes in the tissue reaction. Of particular practical importance is the clearly demonstrated fact that, in most instances, the local application of cortisone is just as effective as the parenteral administration of either ACTH or cortisone. It is of interest that Jones and Meyer (4) have recently reported that the subconjunctival injection of cortisone inhibits the vascularization of the cornea which follows alkali burns.

The most striking effect of these hormones has been in the prompt control of the inflammatory and exudative phases resulting from these various diseases of the conjunctiva and uveal tract. With parenteral treatment there is observed uniformly a subsidence of pericorneal congestion, clearing of the vitreous, diminution of exudates which become more circumscribed, and disappearance of retinal edema. In each instance there has been a concomitant improvement in vision. Experience is as yet limited, but it would seem that the local instillation of cortisone does not influence vitreous exudation or changes in the posterior uveal tract.

In each of the various types of disease presented in this report there is reason to suspect an allergic factor for the inflammatory reaction. Non-granulomatous iritis is at present believed to be a phenomenon of bacterial hypersensitivity; in ocular tuberculosis the inflammatory phase depends upon a sensitivity of the tissues to tuberculo-protein; and, although not conclusive, there is evidence that the pathogenesis

of sympathetic ophthalmia may be a sensitivity to the patient's own uveal tract pigment. The clinical improvement was so dramatic that it was a logical step to study these effects in the experimental animal where many of these ocular phenomena can be faithfully reproduced. The current status of these experimental observations are reported by Dr. Alan Woods and Dr. Ronald M. Wood.

Although clinical experience is of short duration, there are certain practical therapeutic aspects of these observations which should be intensively pursued. Sympathetic ophthalmia is a self limited disease and if the inflammatory reaction can be controlled vision can be saved. The three cases described in this report enjoyed completely successful treatment and, with further experience in the necessary dosage and length of treatment, this should represent a major advance in the preservation of vision in these patients. It has been shown that streptomycin and promizole have a beneficial therapeutic effect on ocular tuberculosis. However, this is not evident for a period of weeks during which time the inflammatory reaction due to hypersensitivity to the products of the tubercle bacillus may cause irreversible tissue damage with consequent visual impairment. The experience thus far suggests that this inflammatory reaction can be successfully controlled with parenteral administration of ACTH or cortisone and by cortisone applied locally when the involvement is limited to the anterior portion of the eye. It seems indicated at present, therefore, to institute hormonal therapy as well as antibiotic administration as soon as the diagnosis is established. It is of further interest that in three of the cases of ocular tuberculosis an almost complete disappearance of the skin hypersensitivity to tuberculin has been demonstrated during the period of ACTH administration.

In view of the experience with ocular tuberculosis explorations have been commenced in the treatment of other clinical situations in which the inflammatory reaction due to tuberculin hypersensitivity may produce serious functional disturbance. A four year old boy was admitted recently with obvious tracheo-bronchial obstruction. There was marked retraction on inspiration with audible wheezing. Bronchoscopy revealed almost total obstruction to the airway by tuberculous granulation tissue. Within three days after ACTH therapy was instituted the inspiratory pattern had become almost normal and a

second bronchoscopic observation on the fourth day revealed a tracheal lumen of normal size.

Since the beginning of these studies several reports have appeared of a preliminary nature describing the effects of ACTH in certain ocular diseases. Gordon and McLean (5) treated six patients with the following diseases: severe corneal edema (corneal dystrophy), secondary glaucoma, chronic irido-cyclitis, retinitis pigmentosa, and acute choroiditis. The response of the patients with irido-cyclitis and choroiditis was dramatic. Olsen and his co-workers (6) studied the effects of ACTH in four patients with acute plastic iritis, two with keratitis and anterior uveal tract diseases and one with chorioretinitis. All patients responded abruptly and favorably. Mann and Markson (7) have reported a case of iritis and episcleritis which cleared completely on ACTH therapy.

Thus, it seems that in most of the cases thus far studied, in whom a favorable response resulted, there was an active inflammatory reaction as the prominent feature. In the studies described in this report the approach was made first in those diseases in which an inflammatory reaction was present thought to be related to some factor of hypersensitivity. It is of interest that in the experiments of Woods and Wood inflammatory reactions set up by chemical agents to which there was no hypersensitivity were blocked. This points the way to a much wider clinical exploration with these hormones and emphasizes the need for precise immunological and biochemical studies of these experimental ocular reactions which provide an important investigative tool for probing the mechanisms of action of ACTH and cortisone

SUMMARY

1. The results of the administration of ACTH and cortisone in two cases of non-granulomatous iritis, in three cases of sympathetic ophthalmia, in five cases of ocular tuberculosis, in one of vernal conjunctivitis, and in two with uveitis following herpes zoster ophthalmicus have been described. The results have been beneficial in each instance, and in those cases with involvement of the anterior portion of the eye cortisone applied locally has been effective.

2. The most striking effect of these hormones has been in the prompt control of the inflammatory and exudative manifestations resulting

from these various diseases of the conjunctiva and uveal tract. With parenteral administration there was observed uniformly a subsidence of pericorneal congestion, clearing of the vitreous, diminution of exudates, and disappearance of retinal edema. Cortisone applied locally has not influenced vitreous exudation or changes in the posterior uveal tract.

ACKNOWLEDGEMENTS

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THE ACTION OF ACTH AND CORTISONE ON EXPERIMENTAL OCULAR INFLAMMATION*

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In the previous communication, experiences with ACTH and cortisone in the treatment of various eye diseases were outlined. It was found that when these agents were injected parenterally they had a profound effect in controlling the inflammatory and exudative phases of such eye diseases as non-granulomatous iritis, sympathetic ophthalmia and tuberculous uveitis. It was also reported that the local or topical use of cortisone in the eye produced a therapeutic effect quite comparable to that noted after the systemic injection of ACTH or cortisone.

At the time the clinical investigation was begun, various experiments were performed in rabbits. These experiments were designed to determine the action of these agents on various forms of ocular inflammation. The eye has certain distinct advantages as an organ in which to study the course and progress of inflammation, permitting an exact evaluation of the degree of ciliary congestion, edema and inflammation of the iris, exudation in the anterior chamber, and the secondary changes of edema, infiltration and vascularization of the cornea. In the course of a long series of experimental studies in ocular tuberculosis (1), a system of giving numerical values to these various inflammatory phenomena, and a final value to the activity of the eye as a whole, has been developed. The final value of inflammatory activity is graded from 0 to a maximum of 4. A trace, or "0.25" represents just a suggestion of ciliary or iris inflammation, while "4" represents the extreme picture of necrosis, caseation and perforation of the globe. This system was followed in the various experiments reported here. As will be noted it permits the preparation of graphs illustrating the degree and course of the inflammatory and exudative reaction.

* The ACTH used in these experiments was supplied by Armour and Co. through the courtesy of Dr. John R. Mote. The Cortisone used was purchased by a grant from the Public Health Service, National Institutes of Health.

When these experiments were first undertaken, we were impressed by two observations. The first of these was that in a study of the effect of ACTH on various allergic diseases, Dr. Harvey and his associates had found there was a marked remission in the clinical symptomatology after the use of ACTH. Second, in the few eye cases thus far treated in which a clinical improvement had been noted, there was reason to suspect an allergic factor in the inflammation. Examples are non-granulomatous iritis, which is believed to be a manifestation of bacterial allergy, sympathetic ophthalmia, in which there is sound reason to believe a hypersensitivity to uveal pigment is related to the pathogenesis of the disease, and tuberculous uveitis where it has been clearly demonstrated that the acute inflammatory phase of the disease is dependent upon a hypersensitiveness to tuberculo-protein. Accordingly, the first experimental attack on the effect of the adrenal cortex hormones on ocular inflammation was a study of their action on recognized ocular allergic reactions. The reactions studied were the ophthalmic reaction to protein agents, the bacterial allergic reaction, and the focal reaction produced in tuberculous eyes by the systemic injection of tuberculin.

The protein anaphylactic reaction was first described by Nicolle and Abt in 1908 (2). These authors found that when guinea pigs were sensitized by the intraperitoneal injection of foreign serum and 32 days later given intraocular injections of the same serum, the animals responded with a definite inflammatory reaction in the eye. Similarly, when guinea pigs were given 1.0 c.c. of horse serum subcutaneously every four days for eight doses, and then given an anterior chamber injection of horse serum, they responded with a violent ocular reaction —conjunctivitis, iritis and hypopyon. Since this early demonstration, the anaphylactic ophthalmic reaction has been used extensively by many investigators as a recognized, easily controlled, experimental reaction.

The bacterial allergic reaction in the eye was first described by Derick and Swift in 1929 (3). These investigators found that a marked tuberculin-like hypersensitiveness could be produced in animals by repeated intracutaneous injections of living Alpha streptococci, or by killed Beta streptococci, and when the cornea of these animals was later scarified and a drop of the specific bacterial antigen instilled in the

eye, an ocular inflammation, characterized by a transient kerato-iritis, developed after 24 hours. This test, with various minor modifications, has also been extensively used in many investigations on bacterial hypersensitivity

The focal reaction produced in tuberculous eyes by the systemic injection of excessive amounts of tuberculin has long been recognized clinically. In 1943 (4), in the course of a study of the effect of desensitization with tuberculin in experimental ocular tuberculosis, it was found that when immune-allergic rabbits with an early secondary ocular tuberculosis produced by the anterior chamber injection of a proper dose of virulent human tubercle bacilli, were given a shocking injection of 100 mgms. of old tuberculin systemically, the diseased eyes responded in 24 hours with a violent inflammatory reaction. This was characterized by pericorneal congestion, evidence of acute iridic inflammation, edema and haziness of the cornea with an increase in vascularization, and sometimes an exudate in the anterior chamber. This reaction was consistently repeated in a large number of animals. Allergic rabbits tolerate tuberculin remarkably well, and this large dose of tuberculin was not attended by collapse, death or other systemic manifestations.

Experiment I. Protein Hypersensitivity. Eight rabbits were sensitized to horse serum by repeated intravenous injection, beginning with 0.5 c.c. of undiluted horse serum on Feb. 8, 1950. Subsequent injections were 0.1 c.c. on Feb. 13, 0.2 c.c. on Feb. 14, 0.5 on Feb. 15, 0.1 c.c. on Feb. 20, 0.2 c.c. on Feb. 21, 0.3 c.c. on Feb. 23, 0.1 c.c. Feb. 27, 0.2 c.c. on Feb. 28, and 0.3 c.c. on March 1.

On March 4th the animals were bled and the anti-horse serum precipitin titer determined. The following titers were obtained: 1:1600, one rabbit; 1:3200, 3 rabbits; 1:6400, 3 rabbits; 1:12,800, one rabbit.

On March 8th, two rabbits having titers of 1:3200 were inoculated in the eyes as follows: The anterior chamber was punctured with a syringe containing 0.2 c.c. undiluted horse serum, the aqueous being withdrawn and the mixture of aqueous and horse serum repeatedly reinjected in the anterior chamber until a thorough mixture had been obtained. The syringe was withdrawn containing the original volume of 0.2 c.c. of a mixture of aqueous and horse serum. This mixture was then similarly injected in the left eye. Estimating the amount of removable aqueous as 0.3 c.c. the amount of horse serum inoculated in the right and left anterior chambers would be 0.08 c.c. and 0.04 c.c. Within 24 hours a full blown non-granulomatous iritis was present in the right eye, and to a lesser extent in the left eye. On a 0–4.0 scale this was estimated as a "2.0" reaction in the right eye and a "1.0" reaction in the left eye. This gradually faded and in eight days

the eyes were entirely white and free of all inflammation. At the same time all eight rabbits were given an intracutaneous injection of 0.1 c.c. of a 1:10 dilution of horse serum in the shaved back. All rabbits showed a marked cutaneous reactivity, erythema and induration appearing in six hours and persisting for approximately 96 hours.

The ocular and cutaneous reactions being thus established, the remaining animals were divided into three groups of two each: a control pair (Group I), containing rabbits with a 1:1600 and a 1:6400 titer, Group II, rabbits with titers of 1:6400 and 1:12,800, and Group III with titers of 1:3200 and 1:6400. Group II was treated with ACTH, the dosage being 2.5 mgms. every 6 hrs. for 48 hours

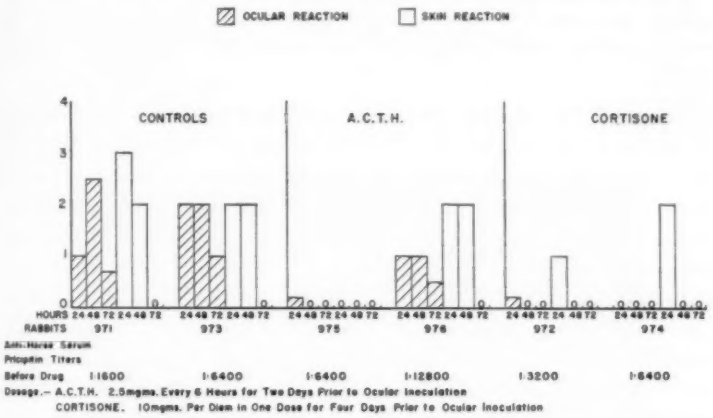
OCULAR REACTION
SKIN REACTION
CONTROLS
A.C.T.H.
CORTISONE
4
3
2
1
0
HOURS 24 48 72 24 48 72 24 48 72 24 48 72 24 48 72 24 48 72 24 48 72 24 48 72 24 48 72 24 48 72
RABBITS 971 973 975 976 972 974
Anti-Horse Serum Precipitin Titers
Before Drug 1:1600 1:6400 1:6400 1:12800 1:3200 1:6400
Dosage.— A.C.T.H. 2.5mgms. Every 6 Hours for Two Days Prior to Ocular Inoculation
CORTISONE. 10mgms. Per Diem in One Dose for Four Days Prior to Ocular Inoculation

FIG. 1. Graph illustrating the blocking effect of ACTH and cortisone on the inflammatory phase of the ophthalmic protein reaction.

prior to inoculation and Group III received 10 mgms. Cortisone acetate *per diem* in one dose for 4 days prior to inoculation. Treatment was continued on Groups II and III rabbits for 48 hours after inoculation. At the cessation of treatment, the rabbits were again bled and the precipitin titer redetermined.

On March 13 after two and four days treatment of Groups II and III, all six rabbits, Groups I, II and III, were inoculated in the anterior chamber of the right eye with 0.1 c.c. horse serum as already described. At the same time a second intracutaneous injection of 1:10 horse serum was given in the back.

Results: The results are shown in Fig. 1. Both untreated rabbits of Group I showed marked ophthalmic reactions coming on after 24 hours and persisting for 11 days. They likewise showed marked cutaneous reactions which persisted for 72 hours.

One rabbit in Group II, treated with ACTH, with a titer of 1:6400 in the blood

serum, showed a minimal traumatic reaction in the eye to the injection which cleared after 24 hours and thereafter the eye remained white and clear. This rabbit showed no reaction to the intracutaneous injection. The second, with a high titer of 1:12,800 showed a moderate ophthalmic reaction which persisted for 72 hours and a full cutaneous reaction.

The Group III rabbits with titers of 1:3200 and 1:6400 showed practically no ophthalmic reaction, one rabbit showing only a minor traumatic reaction while the other showed no reaction of any kind. The rabbit with a titer of 1:3200 showed a slight cutaneous reaction lasting only 24 hours while the second rabbit showed a more marked, but again a transient reaction.

The precipitin titers taken immediately after cessation of treatment were essentially unchanged over the pre-treatment figures. There was no change in the cortisone treated rabbits and a slight drop only in one of the ACTH treated rabbits.

Summary: Two untreated rabbits, sensitized to horse serum, showed marked ophthalmic and cutaneous reactions to the anterior chamber and intracutaneous injection of horse serum. Two similar rabbits were treated with ACTH 48 hours before and 48 hours after inoculation. One of these rabbits showed complete blocking of both the ophthalmic and the cutaneous reactions. The second, an extremely sensitive rabbit with a titer of 1:12,800, showed a partial blocking of the ophthalmic reaction but no blocking of the cutaneous reaction. Two other hypersensitive rabbits were treated with cortisone acetate for 96 hours prior to inoculation and 48 hours after inoculation. Both of these rabbits showed complete blocking of the ophthalmic reaction, but only partial blocking of the cutaneous reaction.

Experiment II. The Quantative Relationship of Treatment to Blocking Action. Sixteen rabbits were sensitized to horse serum by repeated intravenous injections in the same manner as outlined in Experiment I. After a three week period of sensitizing injections, on May 22, all rabbits were bled and the antihorse serum precipitin titer was determined. Eight rabbits showed a titer of 1:1600 and twelve a titer of 1:3200. The rabbits were now divided into four groups of four each of equal antihorse serum precipitin titer. Group I was given 10 mgms. of cortisone in one daily injection for 4 days prior to an anterior chamber injection of horse serum and for seven days thereafter. Group II was similarly given 5 mgms. of cortisone, and Group III 2.5 mgms. Group IV was left untreated as controls. After four days treatment of Groups I, II and III, all rabbits, including the Group IV controls, were given an anterior chamber injection in both eyes of 0.08 c.c. undiluted horse serum. The results of this experiment are shown in Fig. 2.

The four control untreated rabbits all showed violent inflammatory reaction

in the injected eyes. This reaction began within 12 hours after injection with an average intensity of "2". It was characterized by pericorneal congestion, edema and haziness of the cornea, definite inflammatory changes in the iris and a fibrinous exudate in the anterior chamber (Fig. 3). It persisted unchanged for a period of

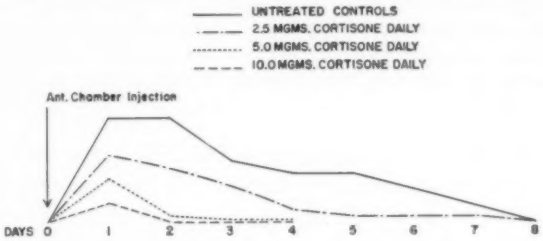
UNTREATED CONTROLS
2.5 MGMS. CORTISONE DAILY
5.0 MGMS. CORTISONE DAILY
10.0 MGMS. CORTISONE DAILY
Ant. Chamber Injection
DAYS 0 1 2 3 4 5 6 7 8

FIG. 2. Graph illustrating the blocking effect of varying amounts of cortisone on the inflammatory phase of the ophthalmic protein reaction.

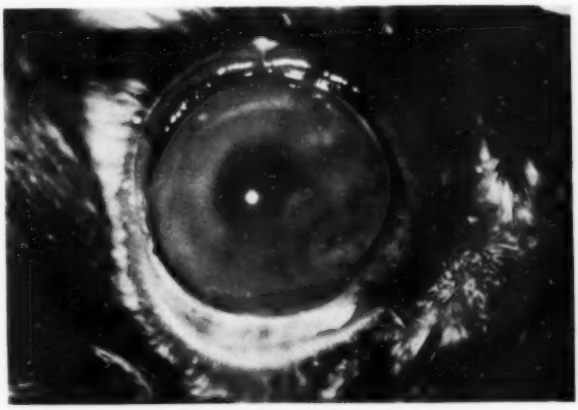

FIG. 3. The protein anaphylactic reaction to horse serum

four days and thereafter gradually declined, and by the seventh or eighth day all eyes were again white without evidence of inflammation.

The animals treated with cortisone behaved quite differently. Of the eight eyes in rabbits receiving 10 mgms. daily, six showed only a minor traumatic reaction of 12 hours duration. The remaining two showed slightly stronger reactions of "0.5," again of 12 hours duration. The eyes thereafter remained white and free of any evidence of reaction during a post-injection period of seven days observation.

Of the eight eyes of the four rabbits receiving 5 mgms. cortisone daily, one eye

showed a minor traumatic reaction only. The remaining seven eyes showed a low-grade transient inflammation, estimated as from "0.5" to "1.0." This reaction was only of 24 hours duration, and thereafter the eyes remained white and free of any evidence of inflammation.

Of the eight eyes of the four rabbits receiving 2.5 mgms. of cortisone, all eyes showed an initial inflammatory reaction of from "0.5" to "2.0." In one animal with the most severe reaction, the inflammation persisted for three days. In the remaining three it was of 48 hours duration. Thereafter all eyes remained white and free of inflammation.

Summary: All eyes of four sensitized rabbits reacted with a violent iritis of eight days duration to the anterior chamber injection of 0.1 c.c. undiluted horse serum. In four rabbits receiving 10 mgms. Cortisone for four days prior to anterior chamber injection and seven days after such injection, this inflammatory reaction was completely blocked in three animals and almost completely blocked in the fourth. In similar animals receiving 5 mgms. of cortisone the reaction was partially blocked and of short duration. In animals receiving 2.5 mgms. cortisone there was decidedly less blocking reaction, the majority of the eyes showing moderate reactions, but of comparatively short duration.

It is quite evident a daily dose of 10 mgms. has an almost complete blocking effect on the inflammatory phase of the ophthalmic protein reaction, and that smaller amounts of the hormone have a comparatively lesser action.

Experiment III-A. Bacterial Hypersensitivity. Eight rabbits received daily intracutaneous injections of 0.1 c.c. of an 18 hour live culture of an Alpha streptococcus from Feb. 9 to March 1st. There developed large cutaneous reactions (20 x 20 mm. erythema and induration) to the later doses, indicating a high sensitivity.

On March 2, two pilot rabbits were given an intra-lamellar injection of 0.005 c.c. of a killed culture suspended in salt solution. There ensued a typical allergic kerato-iritis after 48 hours. This did not fade but merged into a delayed persistent keratitis associated with corneal vascularization which persisted for 16 days before finally fading, leaving a small central corneal scar and a small zone of peripheral vascularization. A quite similar delayed reaction was observed in normal rabbits similarly inoculated. This method of injection therefore seemed unsuitable for a blocking experiment and recourse was had to the corneal scarification technique described by Derick and Swift.

Accordingly, on March 9th, two rabbits were treated with cortisone acetate, 10 mgms. per diem in one dose, and on March 11th, two rabbits were treated with

ACTH, 2.5 mgms. q. 6 hours. Treatment was continued in all four rabbits for 48 hours after inoculation. On March 13, all six rabbits were inoculated in the eyes by the scratch method of corneal scarification with bacterial suspension instilled in the conjunctival sac. At the same time they were inoculated intracutaneously in the shaved back with 0.1 c.c. of a killed bacterial suspension. The untreated control rabbits developed only minimal reactions in the eyes to this method of inoculation which were similar to minimal reactions observed in the four treated rabbits eyes. This experiment was therefore worthless as far as determining any blocking effect on the ophthalmic reaction.

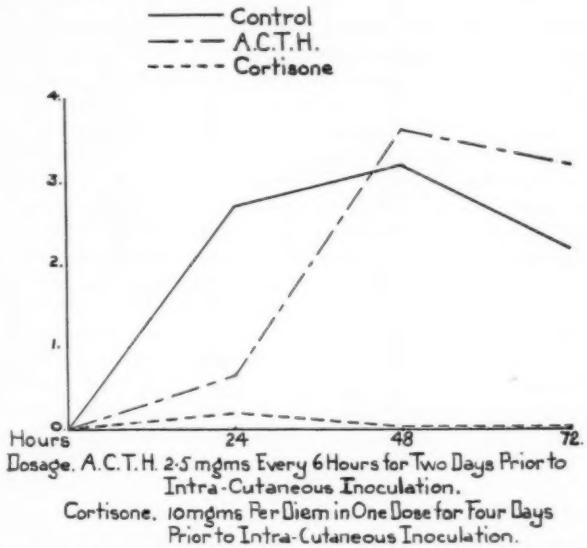

FIG. 4. Graph illustrating the cutaneous reactions to Alpha Streptococci after cortisone treatment.

The cutaneous reactions in these six rabbits are shown in Fig. 4. The untreated control developed full ++ and +++ reactions in 24 and 48 hours. The rabbits treated with ACTH showed a minimal reaction at the end of 24 hours, but a full blown +++ reaction at the end of 48 hours. The rabbits treated with cortisone showed no reaction during 72 hours observation. On March 24th, nine days after treatment with ACTH and cortisone had been discontinued these rabbits were again given an intracutaneous injection of the specific bacterial antigen. All now showed a positive cutaneous sensitivity test with reaction of 5 x 5 and 10 x 10 mm. erythema and induration, all blocking effect of the adrenal cortex hormones having disappeared.

Summary: An experiment designed to produce an ophthalmic reaction in rabbits sensitized to Alpha streptococci was a failure in that no satisfactory reaction was produced in the controls by the method of inoculation employed. The cutaneous reaction in these rabbits was delayed by ACTH administered 48 hours both before and after inoculation, but was not blocked. Cortisone acetate administered 96 hours prior to inoculation, and 48 hours after inoculation, almost completely blocked the cutaneous reaction in two rabbits so treated.

B. Sensitivity to Beta Streptococci: On February 9, 1950, a series of eight rabbits were sensitized by the intracutaneous injection of 0.1 c.c. of a killed, washed 18 hour culture of a Group A Beta-hemolytic streptococcus, suspended in normal salt solution. Similar daily intracutaneous injections were given over a 19 day period. On March 13, two weeks after the last injection all animals were tested for hypersensitivity by the intracutaneous injection of 0.1 c.c. of the specific antigen. All rabbits gave well-marked skin reactions, characterized by erythema varying from 7 x 7 mms. to 15 x 15 mms. with a smaller area of central induration.

In order to determine the maximum dose of killed streptococci the normal eye could tolerate without reaction, six normal rabbits were now given anterior chamber injections of 0.1 c.c. of varying dilutions of a T-50 (spectro-photometer) suspension of killed Beta streptococci. The dilutions injected were 1:20, 1:40, 1:80, 1:160, and 1:320. It was found that the normal eye of an unsensitized rabbit could tolerate 0.1 c.c. of a 1:40 dilution of this suspension without reaction. Stronger dilutions produced a reaction in the eye. This dose, 0.1 c.c. of a 1:40 dilution, was then adopted as the intoxicating dose in the sensitized rabbits. Two sensitized rabbits were now given this injection and both responded with a satisfactory iritis of approximately "2" intensity. On April 13, the cutaneous reactivity of the sensitized animals was redetermined. Beginning April 15, three of the sensitized rabbits were given a daily injection of 10 mgms. of cortisone, the remaining two animals being left untreated. On April 19, all animals, the cortisone treated and controls, were given an anterior chamber injection of 0.1 c.c. of the 1:40 dilution of the streptococcus suspension, and at the same time an intracutaneous injection of 0.1 c.c. of a T-25 concentration of the antigen. Cortisone was continued in the test rabbits for a period of seven days.

The results are shown in Fig. 5. The two control untreated rabbits both showed eye reactions of a maximum of "2", of approximately seven days duration. They likewise showed well marked cutaneous reactions of approximately "1.5" (15 x 15 erythema and central induration). The cortisone treated rabbits behave quite differently. One (993) with a low pre-treatment cutaneous sensitivity, showed no reaction whatsoever to either the anterior chamber or the intracutaneous inoculation. The second (994) with a pre-treatment cutaneous sensitivity of slightly over "1" (10 x 10 erythema and central induration) showed minimal ocular and cutaneous reactions of about 24 hours duration only. The third treated rabbit (995) with

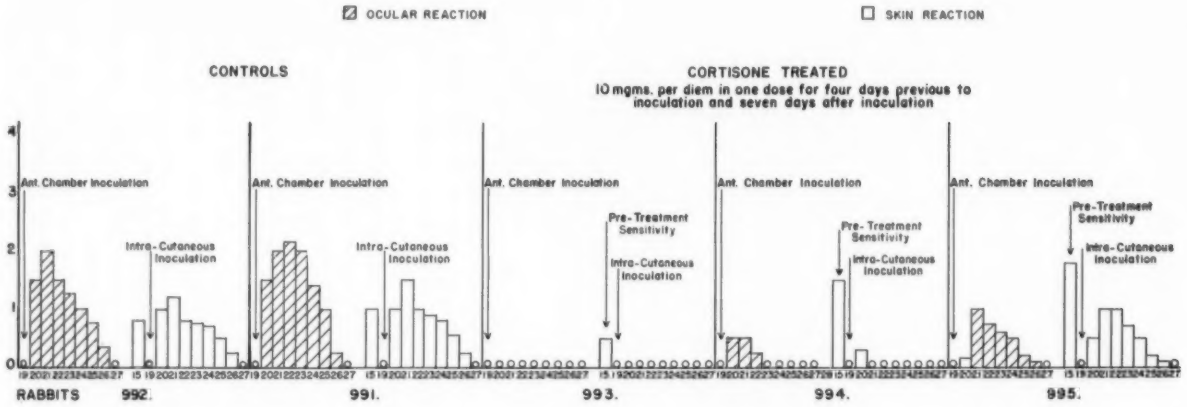

FIG. 5. Graph illustrating the effect of cortisone in blocking ophthalmic and cutaneous reactions to Beta Streptococci in hypersensitive rabbits.

the highest pre-treatment sensitivity showed moderate ocular and cutaneous reactions.

One month after the cessation of treatment, all rabbits, both controls and those formerly treated, were given a second anterior chamber injection and test intracutaneous injection of the streptococcus antigen. All animals now showed marked and equal ophthalmic and cutaneous reactions, all blocking action of the cortisone having disappeared.

Summary: Control, untreated rabbits sensitized to killed beta streptococci showed well-marked ophthalmic and cutaneous reactions to the anterior chamber and intra-cutaneous injection of the specific streptococcus antigen. In similar sensitized and injected rabbits, treated with cortisone prior and subsequent to the test injections the ophthalmic and cutaneous reactions were completely or partially blocked. The degree of blocking appeared somewhat proportionate to the degree of pre-treatment sensitivity.

Experiment IV. The Focal Reaction to Tuberculin. A series of 20 normal rabbits were inoculated subcutaneously with 0.25 c.c. of a six weeks culture of *Mycobacterium tuberculosis var. hominis*, on Dec. 22, 1949. The animals ran the usual asymptomatic course, and on Feb. 5 all were tested for cutaneous hypersensitivity by the intracutaneous injection of 0.1 c.c. of strength 2 P.P.D. All animals reacted with erythema of from 10 x 10 mms. to 20 x 20 mms. with induration. On March 1, all rabbits were given an anterior chamber injection in the right eye of 0.1 c.c. of a six weeks old culture of the same organism diluted to contain about 50 organisms to the oil immersion field. By March 18 all animals showed early evidence of a secondary ocular tuberculosis, with slight pericorneal congestion, minute tubercles in the iris and occasional minor secondary changes in the lens. The cutaneous sensitivity to P.P.D. was now redetermined and recorded. Two test rabbits were now given subcutaneous injections of 100 mgms. of old tuberculin. Both showed violent focal reaction in the diseased eye. The reaction came on after 24 hours and persisted about six days.

The remaining 18 rabbits were now divided into three groups of six each. Group I was left untreated as controls. Group II was treated with ACTH, 10 mgms. per diem in divided doses of 2.5 mgms. every 6 hrs. for four days prior to the shocking dose of tuberculin, and treatment was continued for five days thereafter. Group III was treated with cortisone, 10 mgms. per diem, for four days prior to the shocking dose and for 22 days thereafter. After four days treatment with cortisone and ACTH, all animals, controls and treated, were given a shocking injection of 100 mgms. O.T. subcutaneously.

The controls (Group I) all reacted with a violent ophthalmic reaction, a great increase in the pericorneal congestion, marked inflammatory changes in the iris, and clouding of the cornea with an increase in vascularization (Fig. 6). The ACTH

treated rabbits (Group II) showed decidedly less reaction. Two showed a moderate focal reaction of 2 days duration, two others showed a minimal reaction of 24 hours duration, and the remaining two showed no reaction of any kind. The cortisone treated rabbits (Group III) showed even less reaction, one showing a minimal reaction, while in the remaining five animals the inflammatory reaction was completely blocked, the eyes showing no increase in inflammation after the injection of the O.T. After five days, ACTH was discontinued in the Group II rabbits, but cortisone was continued in the Group III animals.

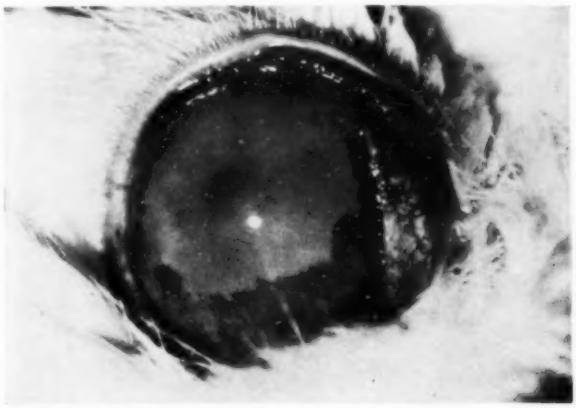

FIG. 6. The focal ophthalmic reaction to tuberculin in immune-allergic rabbits with secondary ocular tuberculosis.

On April 12, two weeks after the ophthalmic reactions had subsided all animals were given a second shocking injection of 100 mgms. of O.T. The eyes of the Controls again reacted, almost as violently as the first time. The eyes of the Group II animals, in whom ACTH had been discontinued two weeks previously, now showed marked focal reactions in three animals while in three the reaction was still completely or partially blocked. The eyes of the Group III rabbits, still under treatment with cortisone, showed minimal traumatic reactions in two instances, while in the others the reaction was completely blocked.

Cortisone was now discontinued and all animals allowed to rest without treatment. Seventeen days later, on May 3rd, all animals were given a third shocking injection of 100 mgms. of O.T. All the control rabbits again reacted, but somewhat less violently than to the previous injection. The Group II rabbits now all showed ophthalmic reactions, of equal intensity as the controls. The Group III rabbits, in whom cortisone had been discontinued for seventeen days, all showed moderate ophthalmic reactions of slightly lesser intensity. All blocking effect on inflamma-

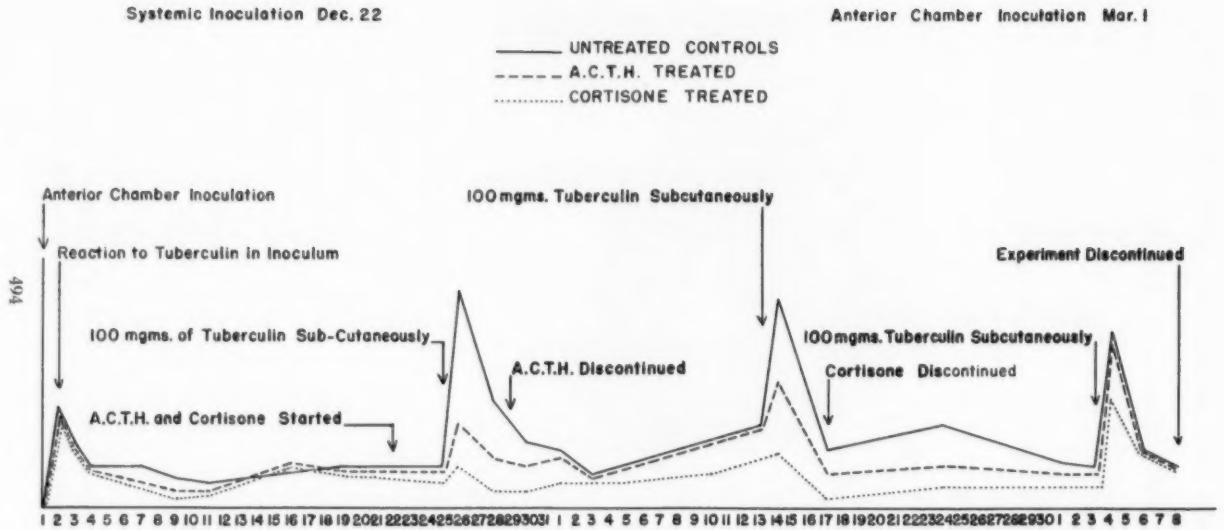
Systemic Inoculation Dec. 22
Anterior Chamber Inoculation Mar. 1
UNTREATED CONTROLS
A.C.T.H. TREATED
CORTISONE TREATED
Anterior Chamber Inoculation
Reaction to Tuberculin in Inoculum
100 mgms. Tuberculin Subcutaneously
Experiment Discontinued
494
100 mgms. of Tuberculin Sub-Cutaneously
A.C.T.H. Discontinued
100 mgms. Tuberculin Subcutaneously
Cortisone Discontinued
A.C.T.H. and Cortisone Started
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 1 2 3 4 5 6 7 8

FIG. 7. Graph illustrating the blocking effect of ACTH and cortisone on the focal ophthalmic to retacion Tuberculin in immune-allergic rabbits with ocular tuberculosis.

tion by both ACTH and cortisone had almost completely disappeared. These results are shown graphically in Fig. 7.

One peculiar phenomenom was noted in the cortisone treated rabbits. While treatment was continued, all traces of inflammatory reaction disappeared from the tuberculous eyes. The tubercles in the iris, however, continued to increase in size and number, presenting the picture of a progressive nodular tuberculosis in an eye utterly devoid of inflammation (Fig. 8).

The effect of ACTH and cortisone on the cutaneous tuberculin reactions could not be evaluated in these rabbits. All rabbits were tested for cutaneous hypersensitivity immediately after the first shocking injection, and at intervals of one

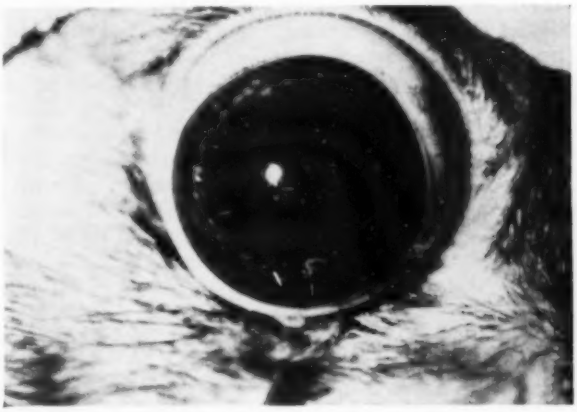

FIG. 8. Progressive secondary tuberculosis in uninflamed eye of immune-allergic rabbit treated with cortisone.

week thereafter. The control, untreated rabbits now gave almost entirely negative reactions and continued to do so after the second and third shocking injections. Quite evidently the injection of the large amounts of tuberculin had had a desensitizing effect, making it impossible to attach any significance to the negative reactions in the controls.

Summary: Treatment with ACTH and cortisone in immune-allergic rabbits prior to a shocking dose of tuberculin, almost completely blocked the inflammatory focal reaction in eyes with a secondary tuberculosis. In both ACTH and cortisone treated animals, this blocking effect completely disappeared about two weeks after cessation of treatment. In rabbits in whom cortisone was continued for

three weeks, the treatment appeared to block the inflammatory phase of the tuberculous process completely but had no effect on the actual progress of the tuberculous lesions.

These four experiments clearly indicate that in the experimental rabbit both ACTH and cortisone have the ability to block the inflammatory phase of the allergic reaction. The question immediately arises whether this ability to block ocular inflammation is confined to inflammation secondary to the hypersensitive reaction, or whether it is similarly manifested in inflammation not related to allergy. This point was investigated by determining the ability of cortisone to block inflammation secondary to irritants.

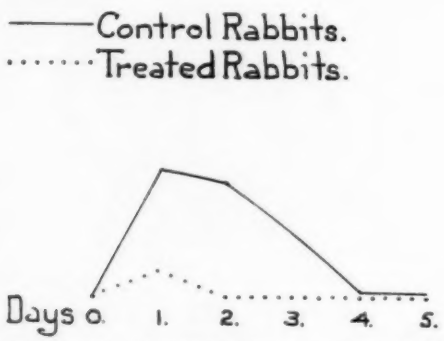

FIG. 9. Graph illustrating blocking effect of cortisone in inflammation produced by injection of glycerin in anterior chamber.

Experiment V. A. In 1931 Seegal and Seegal in the course of experiments on local tissue hypersensitiveness showed that the introduction of such irritants as glycerin, iodine, etc. in the anterior chamber produced a transient iritis.

A series of normal rabbits were injected in the anterior chamber with varying amounts of glycerin. It was found that 0.1 c.c. produced a definite, but transient, iritis of about 3–5 days duration. The majority of such rabbits showed a persistent clouding of the lower portion of the cornea, apparently in the endothelium.

Five normal rabbits were now treated with 10 mgms. of cortisone daily for four days prior to anterior chamber injection and for five days thereafter. After the preliminary treatment these rabbits and five untreated normal rabbits as controls were given an anterior chamber injection of 0.1 c.c. glycerin. The results of this experiment are shown graphically in Fig. 9.

The untreated rabbits all responded with an iritis of moderate intensity, averaging about "1" on the numerical scale. The iritis was of about three days duration,

finally clearing and leaving a slight residual clouding of the lower posterior cornea. Two of the rabbits treated with cortisone showed minor traumatic reactions of 24 hours duration. There was no inflammatory reaction of any kind in the remaining three. All rabbits, however, showed the slight clouding of the lower posterior cornea. This later appeared to be due to a mechanical action of the glycerin on the endothelium.

Summary: The injection of 10 mgms. cortisone a day four days prior to anterior chamber injection, and five days after such injection, completely blocked the inflammatory reaction due to the introduction of glycerin in the anterior chamber.

Experiment V. B. It has long been known that an infusion of jequirity seeds in the conjunctival sac produces a violent conjuntivitis characterized by congestion, chemosis, and a mucopurulent discharge. In fact, many years ago this was a fairly fashionable form of treatment for trachoma, now happily superseded by a more rational therapy. There was no information available on the ocular reaction secondary to anterior chamber injection of jequirity infusion.

A preparation of jequirity[1] was therefore prepared by pulverizing 100 mgms. of jequirity powder, taking it up in 10 c.c. of salt solution, centrifuging five minutes at 500 R.P.M. and syphoning off the supernatant fluid. Various dilutions of this infusion were now injected in the anterior chamber of the eyes of normal rabbits. It was found that the straight infusion and dilutions up to 1:500 caused intense reactions characterized by necrosis of the cornea and often perforation of the eye. It was not until dilutions of 1:2000 were reached that anything resembling a satisfactory iritis was obtained, and the reaction was moderate but occasionally followed by a permanent clouding of the cornea after all inflammation had subsided. Dilutions of 1:4000 gave a low-grade transient iritis from which the animal recovered in about five days without residua. The dose of 0.1 c.c. of a 1:4000 jequirity infusion was adopted as the first test dose.

Six normal rabbits were treated with 10 mgms. of cortisone daily for four days prior to the anterior chamber injection and treatment was continued for a period of four days after injection. After the pre-injection treatment these animals, together with six normal untreated rabbits as controls, were given an anterior chamber injection of a 1:4000 dilution of the jequirity infusion. The controls reacted with a low-grade iritis, which began to subside on the second day. The treated rabbits showed no reaction of any kind. At the end of the second day all rabbits were given a second anterior chamber injection of 0.1 c.c. of a 1:2000 dilution. The untreated control rabbits reacted with an immediate increase in the inflammation, which began to fade on the fourth day and had disappeared by the eleventh day leaving permanently cloudy corneae. The treated rabbits showed

[1] The jequirity used in these experiments was supplied by S. B. Penick and Company through the courtesy of Mr. Richard Hillier.

no immediate reaction of any kind for 48 hours and cortisone treatment was discontinued. Within twenty-four hours after discontinuing the cortisone injections all eyes of the previously treated rabbits developed a mild inflammatory reaction of seven days duration. Three of these six rabbits had the residual corneal opacity shown by the controls. These results are shown graphically in Fig. 10.

Summary: The systemic injection of 10 mgms. of cortisone daily for four days prior to the anterior chamber injection of jequirity infusions completely blocked the inflammatory reaction shown by the controls. When cortisone was discontinued, the previously treated rabbits showed a mild inflammatory reaction of several days duration.

Since both ACTH, which acts through the stimulation of the adrenal cortex to produce endogenous adrenal cortex hormones, and exogenous

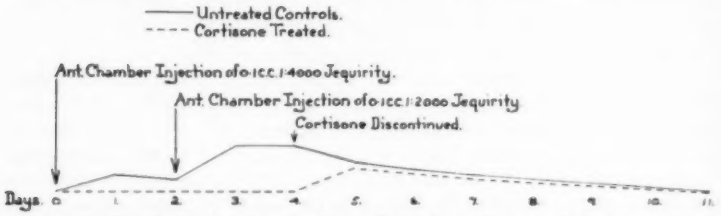

FIG. 10. Graph illustrating blocking effect of cortisone in inflammation produced by injection of jequirity infusion in the anterior chamber.

cortisone administered parenterally, have a similar effect in blocking the inflammatory phase of the hypersensitive reaction, it seems a logical conclusion that cortisone *per se* is at least one if not the most important of the adrenal cortex hormones responsible for this effect. The question therefore immediately arises as to whether this action of cortisone is a direct one on the tissue cells, or is an indirect one through some intermediary agent. The question is admittedly a difficult, if not impossible, one to answer. To determine if cortisone, topically applied, had any effect on control of the inflammatory reaction, the following two experiments were performed.

Experiment VI. Anaphylactic Inflammation. Eight rabbits were sensitized to horse serum in the manner described in Experiments I and II, anti-horse serum titers of 1:1600 to 1:3200 resulting. Four control rabbits were now injected in the anterior chambers with 0.1 c.c of undiluted horse serum, and four were given

anterior chamber injections in the right eye of 0.25 mgms. of cortisone together with 0.1 c.c. of horse serum. In the left eye they were given 1.25 mgms. of cortisone plus 0.1 c.c. of horse serum. The eyes of the control rabbits which received horse serum alone showed a prompt and violent inflammatory reaction of seven days duration. The eyes receiving 0.25 mgms. cortisone plus horse serum showed a low-grade iritis of three days duration. The four eyes receiving 1.25 mgms. of cortisone plus horse serum reacted as follows: One eye showed no reaction of any kind. One eye showed a transient inflammation of "0.5" of twenty-four hours duration. The third eye showed a transient inflammation of "1", appearing on the second day and lasting 24 hours. The fourth eye showed a more marked reaction of "1.5" of forty-eight hours duration. These results are shown graphically in Fig. 11.

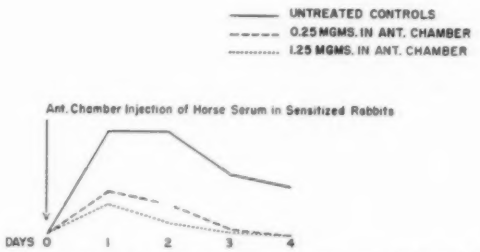

FIG. 11. Graph illustrating blocking effect of cortisone injected in the anterior chamber on the ophthalmic reaction due to sensitization and intoxication with horse serum.

Summary: The anterior chamber injection of 0.25 mgms. of cortisone synchronously with an intoxicating injection of 0.1 c.c. horse serum resulted in a partial blocking of the inflammatory phase of the anaphylactic protein reaction in sensitized rabbits. The injection of 1.25 mgms. cortisone synchronously with the horse serum resulted in a slightly greater blocking effect in similarly sensitized rabbits.

Experiment VII. Jequirity Inflammation. Six normal rabbits were given an anterior chamber injection in both eyes of 1.25 mgms. cortisone plus 0.1 c.c. of a 1:4000 dilution of jequirity infusion. Six control rabbits were given a similar injection of the jequirity infusion alone. The control rabbits reacted with a low-grade iritis. Five of the rabbits receiving the cortisone with the jequerity showed no inflammatory reaction of any kind, while the sixth showed a transient inflammation of "0.5." On the third day these same eyes were again injected with 1.25 mgms. cortisone plus 0.1 c.c. of a 1:2000 dilution of jequirity infusion. The controls were given 0.1 c.c. of the stronger jequirity infusion alone.

The controls all reacted with an immediate exacerbation of the iritis reaching a maximum of "1.0." Eight of the eyes injected with the jequirity plus the cortisone showed no reaction of any kind for first day, while four showed slight reactions. The second day after the injection of the stronger dilution, six eyes showed a moderate reaction, three a trace of beginning inflammation, while three were still negative. By the fifth day ten of the eyes showed well marked inflammation, reaching a peak slightly higher than the untreated control. Thereafter the inflammation rapidly faded and by the seventh day after the anterior chamber injections all eyes were quiet. Seven of them, however, showed the permanent corneal opacity which was present in the controls. These results are shown graphically in Fig. 12.

To confirm the transitory nature of any blocking effect produced by an anterior chamber injection, three normal rabbits were given anterior chamber injections

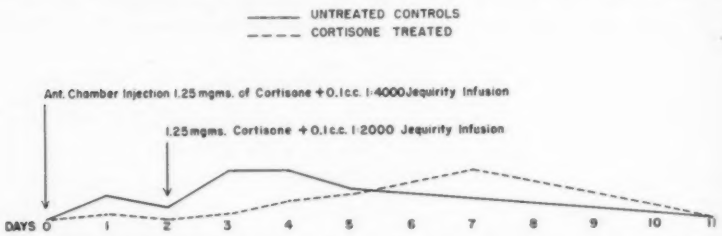
UNTREATED CONTROLS
CORTISONE TREATED
Ant. Chamber Injection 1.25 mgms. of Cortisone + 0.1 c.c. 1:4000 Jequirity Infusion
1.25 mgms. Cortisone + 0.1 c.c. 1:2000 Jequirity Infusion
DAYS 0 1 2 3 4 5 6 7 8 9 10 11

FIG. 12. Graph illustrating blocking effect of cortisone injected in the anterior chamber on inflammation produced by anterior chamber injection of jequirity infusion.

of 1.25 mgms. of cortisone. Three days later the same eyes were given an anterior chamber injection of 0.1 c.c. of a 1:4000 jequirity infusion. All previously treated eyes immediately reacted with an inflammatory reaction equal to the controls.

Summary: The anterior chamber injection of 1.25 mgms. of cortisone completely blocked for two days the inflammation which normally follows the injection of 0.1 c.c. of a 1:4000 dilution of jequirity infusion. It almost completely blocked for a period of twenty-four hours the reaction which follows the injection of a similar amount of a 1:2000 dilution. Thereafter the blocking effect of the anterior chamber injection of cortisone disappeared and ten of the twelve eyes developed a delayed inflammatory reaction. Cortisone injected in the anterior chamber three days before the injection of jequirity infusions had no effect whatsoever on blocking the inflammatory reaction.

COMMENT

The experiments here reported confirm the clinical observations reported elsewhere,—that ACTH and cortisone have a profound effect on certain ocular inflammatory and exudative reactions. It seems quite clear that both ACTH and cortisone administered parenterally can block the inflammatory and exudative phase of the anaphylactic protein reaction in the eye, as well as that of the allergic reaction due to bacterial hypersensitivity, and of the focal reaction produced in tuberculous eyes by the systemic injection of tuberculin, this latter being another example of bacterial allergy. The first and most natural assumption is that in some way these agents inhibit or influence the antigen-antibody reaction. This supposition, however, does not appear valid for the following reasons: a) that the antibody titer is unaffected, b) that when the effect of these agents has worn off the underlying hypersensitive state is found undisturbed, and c) the as yet unreported experiments of Landau and his co-workers, indicate that guinea pigs treated with these agents are still sensitive to histamine shock, and the intestinal muscle of sensitized treated pigs exhibits the Dale phenomenon to the same degree as does that of sensitized untreated pigs. The experiment here reported showing that ACTH and cortisone block the inflammatory reaction due to irritants equally as well as they block inflammation secondary to the hypersensitive reaction, is also evidence that their action in blocking inflammation, is independent of any effect on the antigen-antibody reaction.

In the dosage employed in these experiments, exogenous cortisone administered parenterally, blocked inflammation and exudation in the rabbit's eye equally as well as, or even better than ACTH. It is generally accepted that the action of ACTH is chiefly through its stimulation of the adrenal cortex resulting in the production of endogenous adrenal hormone. The fact that ACTH was slightly less efficacious in the rabbit than was cortisone might have been due to the dosage employed, or possibly that the adrenal cortex of the rabbit may not be especially susceptible to stimulation by ACTH of porcine origin. There is as yet no clear-cut demonstration of the mechanism whereby cortisone exerts its effect on inflammation and exudation. The clinical demonstration that cortisone 1 c.c./25 mgms. locally applied into the con-

junctival sac has a similar, though slightly delayed, blocking effect on inflammation, suggests that it acts in the same manner directly on the superficial tissue cells as on the vascular and lymphatic apparatus of the inner eye. The further demonstration, here reported, that cortisone injected in the anterior chamber has an immediate blocking effect on inflammation produced by such agents as jequirity and glycerin, strengthens the assumption that it acts directly, rather than by some intermediary mechanism.

It was interesting that in these experiments, the action of cortisone and ACTH in blocking the inflammation and exudation secondary to the anaphylactic and allergic reaction was much more evident in the eye than in the skin. We have already observed that the eye, with its rich supply of vascular and nervous tissues, all tightly enclosed in a comparatively avascular tissue of sclera and cornea, is a capital place to observe and follow the course of an inflammatory reaction. Perhaps its very isolation permits more specific reactions than is possible in such a cosmopolitan and universal structure as the skin. Certainly, however, the inhibitory effect was more clear-cut in the eye than in the skin.

It has been shown in these experiments that the action of ACTH and cortisone in blocking inflammation and exudation is only temporary. In inflammation secondary to the hypersensitive state when the rabbits were tested two weeks after treatment with ACTH or cortisone had been discontinued, they were normally sensitive to contact with the specific antigen and reacted in the classical manner. Further, in experiments with jequirity, it was shown that cortisone injected locally three days previously in no way blocked or lessened the inflammation secondary to the later anterior chamber injections of jequirity. In the case of animals receiving cortisone parenterally, anterior chamber injections of jequirity did not give rise to inflammation. However, 24 hours after the parenteral administration had been discontinued in these animals the eyes became inflamed. Likewise, one anterior chamber injection of 1.25 mgms. cortisone given simultaneously with the jequirity, protected the eye for only 24–48 hours. All this would indicate that since these agents cannot be used indefinitely, their clinical efficacy would be greatest in such ocular diseases as are in their very nature self-limiting. Such conditions would be non-granulomatous iritis, allergic keratitis, and sympathetic ophthalmia. They should also be of

value in certain granulomatous diseases such as tuberculosis, where there is an inflammatory and destructive phase due to tissue hypersensitivity. In such conditions it is possible they might block the destructive inflammatory phase sufficiently long to allow the normal defense mechanism of the body to take over, or appropriate anti-biotic and sulfone therapy to exert their specific effect. In the limited clinical experience to date, it has been precisely in these conditions the most dramatic effect has been observed. It should be noted, however, that as yet there is no clinical or experimental evidence of any action of these agents in blocking ocular inflammation, tissue destruction, or disease due to bacterial infection. In one experiment here reported, it was noted that the number and size of iris tubercles continued to increase while all external inflammation was controlled. This would indicate that the action of cortisone was on the inflammatory mechanism *per se* and not on the underlying disease process.

SUMMARY

1. Cortisone and ACTH injected parenterally have a profound effect on the inflammatory phase of the hypersensitive reaction, blocking the inflammation and exudation which occurs in the ocular protein anaphylactic reaction, the ophthalmic reaction secondary to bacterial allergy, and the focal reaction in tuberculous eyes.

2. Cortisone and ACTH block effectively the inflammatory reaction in the eye produced by glycerin and jequirity infusion.

3. Cortisone injected locally in the anterior chamber has an immediate but temporary effect in blocking the inflammatory phase of the protein anaphylactic reaction in the eye, and the inflammatory reaction secondary to the anterior chamber injection of glycerin and jequirity.

4. The accumulated clinical and experimental evidence of the effect of cortisone on ocular inflammation suggests that its effect may be due to a direct action on the local mesenchymal tissue.

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CORTISONE IN EXPERIMENTAL SYPHILIS (A PRELIMINARY NOTE)[1, 2]

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Administration of cortisone (1.5–3.0 mg. per K twice daily) to 32 rabbits with intradermal syphilomas and 4 animals with intratesticular lesions induced a striking alteration in the course of the infection; 14 animals served as controls. The Nichols strain of *Treponema pallidum* was used throughout.

When cortisone was given to rabbits with typical erythematous indurated dermal syphilomas, the lesions within 48 hours became slightly smaller, pale, soft and spongy, and filled with a tenacious mucoid material, tentatively identified as hyaluronic acid on the basis of hyaluronidase action.[3] Lesions which first appeared during cortisone therapy were similar.

The lesions enlarged slowly but steadily while the drug was being administered. With prolonged administration (15–25 days) the surface of the lesion ruptured with extrusion of the mucoid material. Darkfield examination of this material showed actively motile *T. pallidum* in much larger numbers than were found in control lesions. The treponemes were shown to be virulent by animal passage, and were susceptible to the immobilizing action of specific immune serum (1).

Withdrawal of cortisone was followed in 2–7 days by a "rebound" phenomenon characterized by the re-appearance of erythema and induration, and rapid enlargement of the lesions to a size much larger than that of the controls. The rebound was noted regardless of the stage of evolution of the syphiloma at which cortisone therapy was

[1] These studies were supported by a grant from the Division of Research Grants and Fellowships of the National Institutes of Health.

[2] The cortisone used in these experiments was kindly supplied by Merck and Company, as CORTONE, a brand of cortisone acetate.

[3] In 2 animals with well developed syphilomas ACTH (1.0 mg. per K) given every 8 hours for 15 doses produced essentially the same changes as those induced by cortisone. The ACTH used in these experiments was kindly supplied by Armour and Company.

started. Spontaneous resolution of the lesions eventually occurred, as in the controls.

Essentially the same changes as those described above were noted in testicular syphilomas under the influence of cortisone.

FIG. 1a. Section of syphiloma from Rabbit 29-64 inoculated intradermally with 500 *T. pallidum* at each of 4 sites on 5-18-50. Lesions appeared on 6-6-50. No cortisone was given. Biopsy 6-17-50.

Sections of lesions from cortisone treated animals showed large rather well demarcated areas of poorly staining material with relatively few cells; in contrast to control lesions which showed the usual intense mononuclear cell infiltration, interspersed with small amounts of this acellular material. Photomicrographs of representative lesions are shown in Figure 1. Serial biopsies on animals before, during, and after

cortisone therapy likewise showed a decrease in inflammatory cells and marked increase in the acellular material during treatment; with a return to the more usual picture following discontinuance of cortisone.

FIG. 1b. Section of dermal syphiloma from Rabbit 29–67 inoculated same day with same material. Lesions appeared 6-5-50. Cortisone 3.0 mg./K administered twice daily for 10 doses beginning 6-12-50. Biopsy 6-17-50.

In a small series of rabbits given cortisone over a period of 2–5 weeks the titer of Wassermann reagin was significantly lower than in control animals simultaneously inoculated but not given cortisone. On the other hand, preliminary titrations of immobilizing antibody have shown no essential difference from control animals.

Treponemes in the lesions of cortisone treated animals are susceptible to the action of penicillin; however, in the cortisone treated animals

large numbers of dead treponemes are present 24 and 48 hours after penicillin therapy, unlike controls in which no spirochetes whatever are usually seen after 24 hours (2).

DISCUSSION

The familiar picture of the evolution of experimental syphilis in the rabbit is a product of the complex interaction of spirochete and host. Under the influence of cortisone this interaction is sufficiently altered to produce in a sense a dissociation of parasite and host. The ordinary response of the host to large numbers of treponemes is partially suppressed, while at the same time treponemes are multiplying in an unrestrained manner. This effect may be basically analogous to those reported by Finland, Kass, and Ingbar (3) in pneumococcal pneumonia, and by Berthrong, Rich, and Griffith (4) and Harris and Harris (5), in the hypersensitive state.

Determination of 1) the source of the hyaluronic acid which accumulates in excessive amounts along with the multiplication of *T. pallidum*; 2) the influence of cortisone on the hyaluronic acid-chondroitin system; and 3) the relationship of these changes to the development of Wassermann reagin should prove to be fruitful fields of investigation (6, 7).

From a practical point of view, until more is known about the effect of cortisone on the host-parasite relationship in syphilis it would seem unwise to give the drug to patients with this disease. A "rebound" phenomenon in man could be particularly dangerous, for example in syphilitic involvement of the coronary arteries.

SUMMARY

Under the influence of cortisone therapy, syphilomas induced in rabbits by intradermal or intratesticular inoculation of *Treponema pallidum* show striking alterations from the picture usually observed in experimental syphilis, in that the lesions become soft and spongy, there is an excessive accummulation of a mucoid material tentatively identified as hyaluronic acid, treponemes are unusually abundant, and the production of Wassermann reagin seems to be inhibited. Upon withdrawal of cortisone there is a rebound phenomenon in which the lesions reach an unusual size.

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